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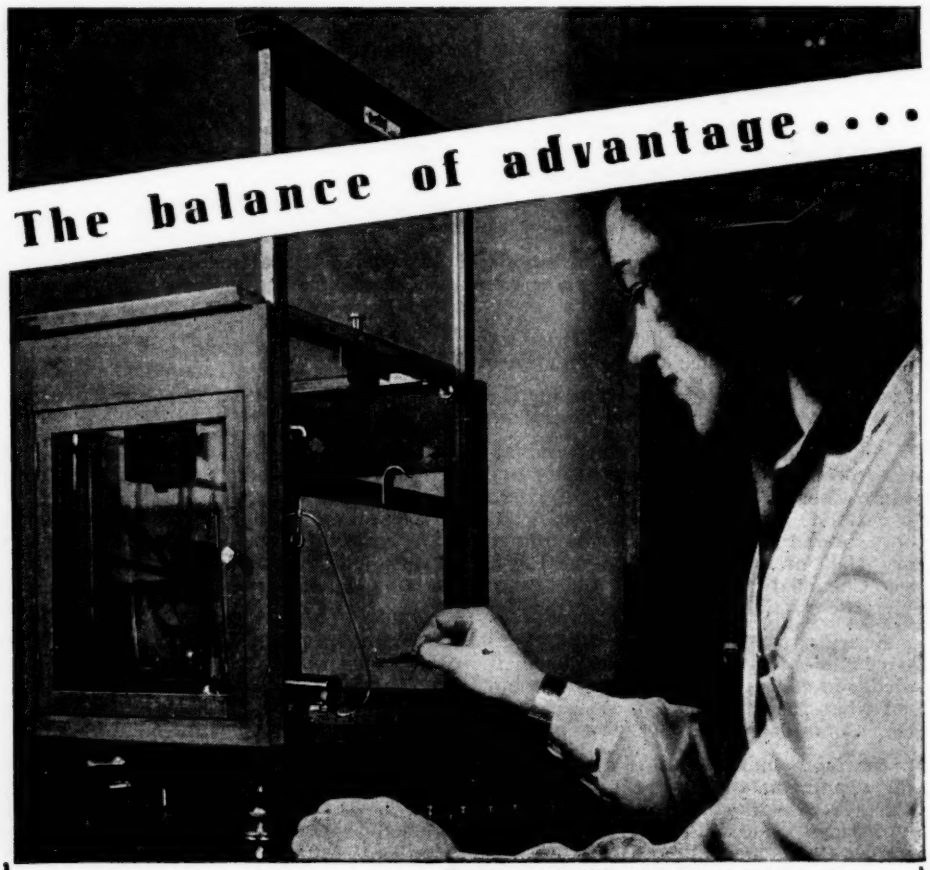

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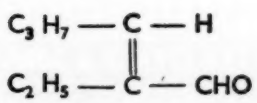

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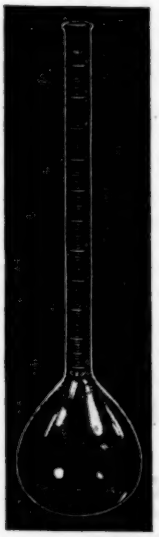

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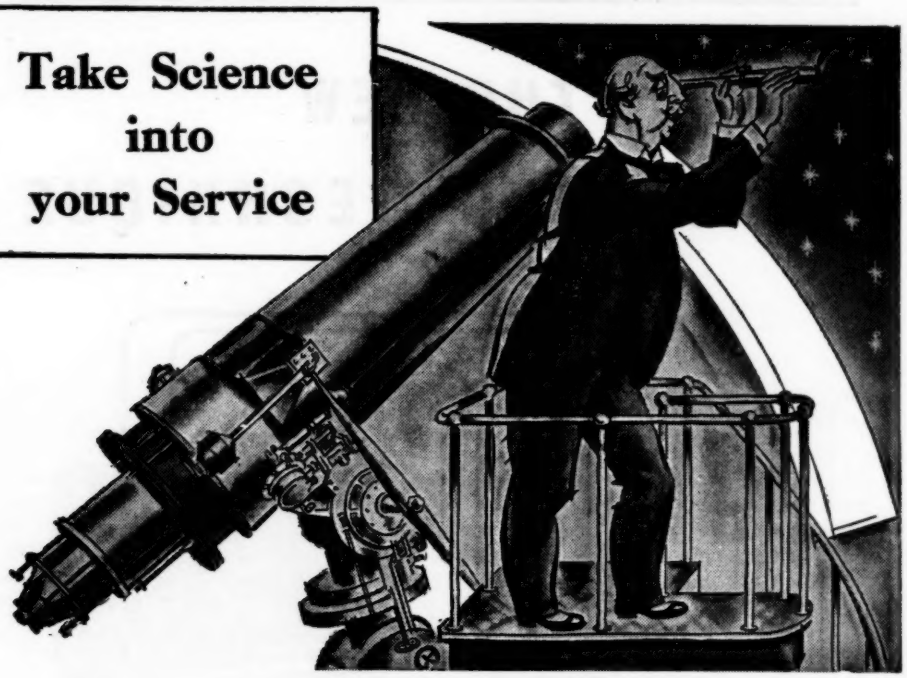

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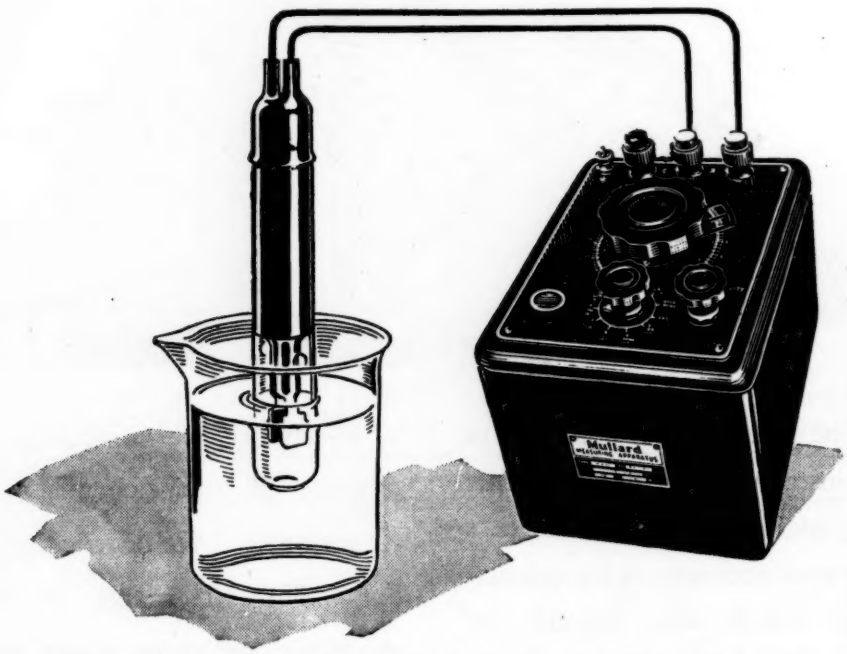

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1. *The Oxidation of β-Carotene in Solution by Oxygen.*

By R. F. Hunter and R. M. Krakenberger.

Examination of the products formed by oxidation of solutions of β-carotene in arachis oil and benzene by oxygen indicates that this proceeds by way of attack of the first and then the second terminal double bond of the conjugated system.

Although it is well known that the carotenes undergo rapid oxidation in contact with air, little is known of the reactions involved other than that they lead to ultimate loss of colour with gain in weight and increased solubility. It has been shown by Baur (*Helv. Chim. Acta*, 1936, **19**, 210; 1937, **20**, 402) that ultra-violet irradiation of α-carotene in chloroform causes initial rapid autocatalysed absorption of oxygen with deepening of colour followed by further absorption, independent of light, leading to loss of colour. The first stage is reversible and is probably connected with the formation of dipole association products (cf. von Halban, Briegleb, *et al.*, *Z. physikal. Chem.*, 1925, **117**, 461; 1932, *B*, **19**, 255; 1934, **27**, 161; Hunter, Qureishy, and Samuel, *J.*, 1936, 1576). It is evident that the early stages of actual oxidation of carotene by air will involve attack of the extended conjugated system which might be expected to commence at one of the terminal double bonds of the β-ionone ring, since resonance should cause progressive loss of " double-bonded character " towards the centre of the system (Zechmeister, Le Rosen, Schroeder, Polgar, and Pauling, *J. Amer. Chem. Soc.*, 1943, **65**, 1940). This has been borne out by an examination of the oxidation of β-carotene by oxygen both in arachis oil and in benzene.

The experiment on the oxidation of β-carotene in arachis oil by oxygen was carried out at 50°. The progress of oxidation was followed by determination of E (1%, 1 cm.) values at the highest carotene absorption band and by a limited number of chromatographic analyses. As will be seen from Table I, oxidation proceeded at a much slower rate than might have been anticipated on *a priori* grounds.

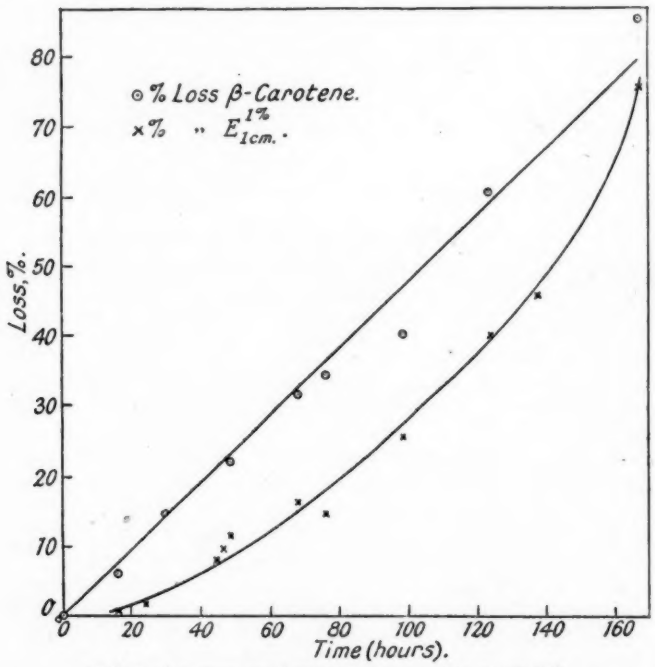
Table I.

Oxidation of β-carotene in arachis oil at 50°.

	Carotene content (50 g. of oil) :			E (1%, 1cm.) at 464 mμ.		
Time (hrs.).	Initial.	After oxidation.	Loss, %.	Initial.	After oxidation.	Loss, %.
16	0·0568	0·0529	6·0	2·61	2·59	0·8
24	—	—	—	2·61	2·57	1·5
30	0·0489	0·0418	14·5	—	—	—
45	—	—	—	2·61	2·40	8·1
46½	—	—	—	3·86	3·48	9·8
49	0·0839	0·0654	22·0	3·86	3·42	11·4
69	0·0722	0·0493	31·7	3·32	2·79	16·1
77	0·0568	0·0374	34·2	2·61	2·23	14·6
99½	0·0359	0·0214	40·3	1·65	1·12	25·5
125	0·0359	0·0140	60·9	1·65	0·988	40·1
138½	—	—	—	2·46	1·34	46·0
168	0·0489	0·0698	85·8	2·46	0·69	75·9

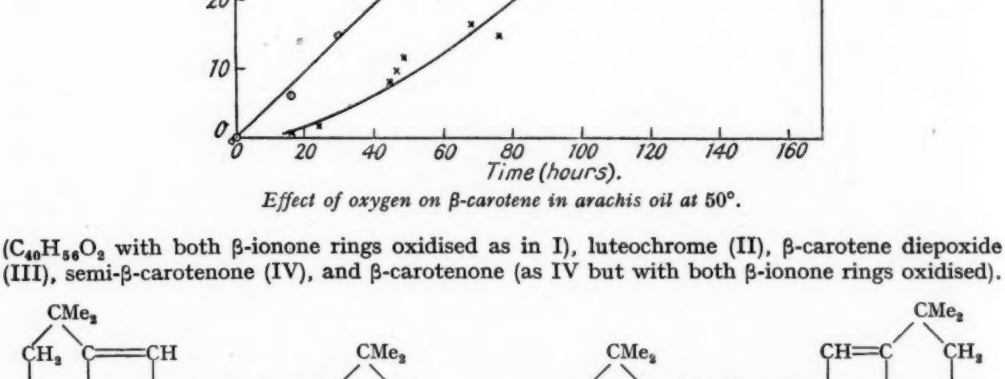
After 212 hours, complete bleaching had taken place. The comparison of the % loss of carotene and % loss in E(1%, 1 cm.) at 464 mμ with time is shown in the diagram. The former appears to be in simple proportion, but the loss of E(1%, 1 cm.) value increases with time owing, evidently, to the disappearance of oxidised carotenes having absorption spectra similar to that of β-carotene itself.

Chromatographic separation of the unsaponifiable matter obtained from "oxidised" solutions of β-carotene in arachis oil furnished carotenoids having the spectroscopic characteristics of mutatochrome (I) (Karrer and Jucker, *Helv. Chim. Acta*, 1945, **28**, 427; formerly regarded as "β-carotene oxide," Euler, Karrer, and Walker, *ibid.*, 1932, **15**, 1507), aurochrome



Effect of oxygen on β-carotene in arachis oil at 50°.

($C_{40}H_{56}O_2$ with both β-ionone rings oxidised as in I), luteochrome (II), β-carotene diepoxide (III), semi-β-carotenone (IV), and β-carotenone (as IV but with both β-ionone rings oxidised).



[$C_{18}H_{22}$ = ·CMe:CH·CH:CH·CMe:CH·CH:CH·CH:CMe·CH:CH·CH:CMe·.]

Evidence was also obtained of the presence of β-carotene epoxide (as III, but with only one β-ionone ring oxidised).

A similar experiment, in which a solution of β-carotene in benzene was treated with oxygen at 50°, provided a striking contrast in the rate of oxidation, as indicated in Table II. The difference is evidently attributable to the presence of the natural anti-oxidant and unsaturated glycerides in arachis oil. Chromatographic separation of the products of oxidation furnished carotenoids having the spectroscopic characteristics of β-carotene epoxide, mutatochrome (I), luteochrome (II), and semi-β-carotenone (IV). The course of oxidation of β-carotene by oxygen followed in arachis oil and in benzene is therefore similar, and evidently consists in

TABLE II.

Time (hrs.).	E(1%, 1 cm.) at 464 mμ.	β-Carotene (g./100 c.c.).	Loss, %: in E (1%, 1 cm.).	Loss, %: in carotene.
0	3·19	0·134	0	0
2	3·12	0·134	2·2	0
4	3·03	0·132	5·0	1·9
6	2·73	0·105	14·4	22·0
8	1·50	0·062	53·0	54·2
24	0	0	100	100

attack on a terminal double bond to give β-carotene epoxide which is converted in the presence of acid into mutatochrome, which then undergoes fission to yield semi-β-carotenone; and a similar attack of the second β-ionone ring leading to the production of luteochrome, aurochrome, and β-carotenone.

EXPERIMENTAL.

Oxidation in Arachis Oil.—(i) A solution of β-carotene [0·53 g., E(1%, 1 cm.) = 2120 at 464 mμ in benzene] in warm benzene (8 c.c.) was gradually diluted with fresh deodorised refined arachis oil (*ca.* 500 g.), and the resulting solution was heated at 50° under reduced carbon dioxide pressure for 10 minutes in order to remove as much benzene as possible without causing very substantial *cis*-isomerisation. The resulting solution, which had E(1%, 1 cm.) 2·61 at 463 mμ in benzene on the Hilger–Nutting spectrophotometer, was stored in carbon dioxide.

A carotene estimation was made by saponification of the oil (50 g.) with potassium hydroxide (15 g.), water (25 c.c.), alcohol (75 c.c.), and light petroleum (50 c.c.) for 2—2½ hours and chromatographic separation of the petrol-soluble unsaponifiable matter on Savory and Moore's " Mayfair " alumina under slight carbon dioxide pressure, with the usual precautions (Hunter and Scott, *Biochem. J.*, 1941, **35**, 31; 1944, **38**, 212). The carotene zone was eluted with ether–benzene–absolute alcohol. The residue obtained by evaporation under reduced carbon dioxide pressure furnished a residue whose solution in benzene had a log I_0/I value corresponding to 0·0568 g. of β-carotene [the E(1%, 1 cm.) value of 2·61 for the oil corresponds to a β-carotene content of 0·1135%].

Portions of about 55 g. of this solution (or other similarly prepared solutions) were treated with a stream of oxygen at 50° for periods ranging from 16 to 212 hours. The E(1%, 1 cm.) value in benzene at 463 mμ of the oxidised sample was determined on the Hilger–Nutting spectrophotometer, and 50 g. of the remainder were assayed for carotene by chromatographic separation in which the *cis*-isomers were included with the all-*trans*-β-carotene.

(ii) The products formed during oxidation were examined in the cases of solutions in arachis oil which had been treated with oxygen for 99½ and 10 hours (corresponding to carotene losses of 40 and 3%, respectively). Two experiments were made with regard to the more prolonged oxidation. In each case, 500 g. of a solution of β-carotene (*ca.* 0·5 g.) in arachis oil were kept at 50° in a thermostat during the passage of a stream of oxygen. The resulting oil was saponified in the usual way and extracted with light petrol and thereafter with ether, and the combined extracts were washed, dried (Na_2SO_4), and evaporated with the usual precautions, and the residue chromatographed on " Mayfair " alumina. The chromatogram was divided into 3 or 4 groups of zones which were separately rechromatographed.

The first experiment (99½ hours) furnished a chromatogram of some 14 zones, the lowest of which contained β-carotene, and the three upper zones oxidised carotenoids with the following spectroscopic characteristics: Zone 14, abs. max. at 447 and 427 mμ; zone 13, abs. max. at 447 and 427 mμ; zone 12, abs. max. at 451 and 431 mμ in carbon disulphide (maxima at 620, 600, 590, and 632 mμ respectively in the antimony trichloride reaction). Zone 8 furnished a carotenoid having the spectroscopic characteristics of aurochrome (abs. max. at 457 and 428 mμ in carbon disulphide and at 587 mμ in the antimony trichloride reaction), and zone 4 yielded a carotenoid corresponding to mutatochrome (abs. max. at 486, 458, and 428 mμ in carbon disulphide and at 595 mμ in the antimony trichloride reaction). Zone 2 furnished material having spectroscopic characteristics close to those of β-carotene epoxide.

In a second and similar experiment, zones containing carotenoids having the spectroscopic characteristics of luteochrome (abs. max. at 480, 451, and 419 mμ in carbon disulphide) and β-carotenone (abs. max. at 536, 497, and 466 mμ) were also obtained. In this case, a small quantity of crystalline mutatochrome was isolated from the appropriate zone.

In the third experiment (10 hours), the chromatogram furnished zones containing carotenoids having the spectroscopic characteristics of mutatochrome (abs. max. at 485, 457, and 428 mμ), β-carotenone (539, 499, 474, and 448 mμ), β-carotene epoxide (512, 482, and 452 mμ), and semi-β-carotenone (538, 499, and 465 mμ in carbon disulphide). This chromatogram differed from those of the previous experiments in that it was more weakly coloured and the absorption spectra of the oxidation products were more sharply defined.

Oxidation in Benzene.—(i) A solution of β-carotene (200 c.c.), prepared from β-carotene [E(1%, 1 cm.) = 2100; *ca.* 0·5 g.] and benzene (" AnalaR," Towers, 500 c.c.) in a vessel fitted with a reflux, was treated at 50° (thermostat) with a stream of oxygen (previously saturated with benzene by passage through a bubbler containing the solvent) at a fixed rate. At intervals, 2-c.c. and 25-c.c. samples were withdrawn and examined with respect to E(1%, 1 cm.) value and carotene content, the latter being separated by chromatography on alumina after dilution with light petrol and spectroscopically determined in the usual way.

(ii) A solution of β-carotene [E(1%, 1 cm.) = 2350; *ca.* 1·5 g.] in purified benzene (1000 c.c.) was treated with a slow stream of oxygen at 50° for 5 hours, during which the E(1%, 1 cm.) value decreased from 3·65 to 3·1. The solution was evaporated under reduced carbon dioxide pressure with the usual

precautions and the residue was chromatographed on "Mayfair" alumina. The chromatogram consisted of 17 zones which furnished substances having the following spectroscopic characteristics:

Zone.	Colour.	Abs. max. (mμ) in CS_2.	$SbCl_3$ reaction.
17	Orange	Vague	Vague, 599 mμ. Greenish
16	Pink	,,	Green
15	Yellow	512, *481*, 457	588 and 494 mμ. Blue-grey
14	Pink	483, 458	Blue ⟶ green
13	Red	484, *469*	Mauve ⟶ green
12	Orange-yellow	Vague	*728*, *667*, 595, and 479 mμ. Green
11	Orange	,,	481 mμ. Green
10	Pink	,,	637, 585, *493* mμ. Green
9	Fawn	,,	588 mμ. Deep blue
8	Canary-yellow	482, 456	—
7	Lemon-yellow	486, *453*	640 and 597 mμ. Blue
6	Yellow	474, *451*	*662* and 592 mμ. Blue
5	Orange	510, 480, 458	585 mμ. Blue
4	Pink	536, 502, 468	585 mμ. Violet
3	Pink	538, 503, 470	588 mμ. Violet-blue
2	Pink	532, 499, 468	586 mμ. Violet
1	Orange	527, 494, 465	*663* mμ. Blue-green

The spectroscopic characteristics of zones 1—4 correspond to semi-β-carotenone and oxy-semi-β-carotenone, those of zone 5 to β-carotene epoxide, of zone 7 to mutatochrome, and of zone 14 to luteochrome.

We thank the Directors of Lever Brothers and Unilever Limited for permission to publish these results.

RESEARCH DEPARTMENT, LEVER BROTHERS AND UNILEVER LTD.,
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2. *The Configuration of Heterocyclic Compounds. Part XI. Preparation of Phenoxstibines and Resolution of* 10-p-*Carboxyphenyl*-2-*methylphenoxstibine.*

By (MISS) I. G. M. CAMPBELL.

The preparation of several phenoxstibines by the reaction of phenylstibinous halides on the "double" Grignard reagent from 2 : 2′-dibromo-4-methyldiphenyl ether is described. The resolution of 10-*p*-carboxyphenyl-2-methylphenoxstibine has been accomplished by means of the strychnine salts, and the *d*- and the *l*-acid, $[\alpha]_D \pm 77°$ in chloroform, are stable in chloroform and benzene at the boiling point but racemise slowly in boiling alcohol. These results indicate that the molecule is folded about the O–Sb axis in order to accommodate the intervalency angle of antimony, and that the folding is sufficiently rigid to produce optical isomers of considerable stability. The *dl*-acid was tested for trypanocidal properties and was shown to possess little activity compared with "stibophen."

PARTS I—X of this series (Turner, Lesslie *et al.*, *J.*, 1934, 1170; 1935, 1051, 1268; 1936, 730; 1937, 444; 1938, 29, 37, 404, 1001; 1939, 1050) describe the resolution of phenoxarsines and the unsuccessful attempts to resolve phenox-thionine-, -selenine-, -tellurine-, and -thianthren-carboxylic acids. To explain these results it was suggested that the phenoxarsine molecule was rigidly folded about the O–As axis, whereas the other molecules, though folded, were flexible. The stability of the optically active phenoxarsines was ascribed to the mutual effect of the folded ring system and the third group attached to the tervalent arsenic atom. It was considered probable that phenoxstibines would exhibit similar stability and that it would be of interest to compare the two types of compound, especially as the stereochemistry of antimony compounds has been little studied.

Although much information has been obtained on the stereochemistry of 3-covalent nitrogen, phosphorus, and arsenic by both physical and organic methods, evidence for the configuration of 3-covalent antimony compounds is relatively meagre. *X*-Ray methods have been used to elucidate the structure of metallic antimony and some of its inorganic compounds, and the trihalides have been studied in the vapour state by electron diffraction, but little information on tervalent organic antimony compounds is available. No attempted resolution of antimony compounds has been reported.

Physical measurements show that the molecules of antimony trihalides are pyramidal with

interbond angles of about 100°, and that in quinquevalent compounds such as the trimethylstibine dihalides the molecule has the form of a trigonal bipyramid with the antimony atom and the three methyl groups in the central plane and the halogens at the two remaining apices (Wells, *Z. Krist.*, 1938, **99**, 367). The dipole moment of triphenylstibine dichloride is zero (*Z. anorg. Chem.*, 1943, **250**, 257; cf. *J. Amer. Chem. Soc.*, 1942, **64**, 173), which confirms the bipyramidal structure for compounds of this type. The dipole moments of triphenyl-phosphine, -arsine, and -stibine are 1·45, 1·07, and $0·57 \times 10^{-18}$ e.s.u. respectively, suggesting a progressive reduction in the height of the pyramidal molecule (*Z. physikal. Chem.*, 1932, *B*, **19**, 401). As it seemed unlikely that resolution of a simple stibine containing three different groups would be successful unless the inversion of this pyramidal configuration was greatly inhibited, it was decided to attempt the resolution of a phenoxstibine (I) where the antimony atom was a member of a heterocyclic ring.

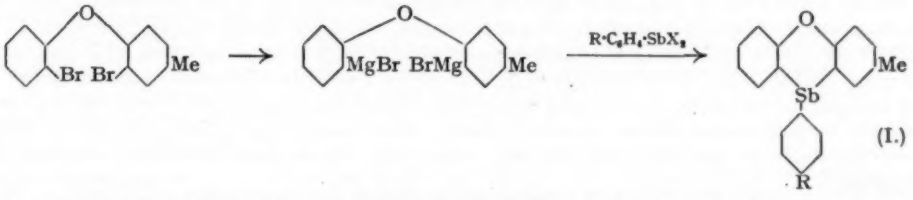
The resolution of several phenoxarsinecarboxylic acids into optically stable enantiomers (Lesslie and Turner, *loc. cit.*) and the isolation of two geometrical isomers of 5 : 10-di-*p*-tolyl-5 : 10-dihydroarsanthren (Chatt and Mann, *J.*, 1940, 1184) leave little doubt that this type of molecule is folded about the central axis. One can suggest an approximate configuration for the molecule by calculation from the geometry of the figure. The radii of aromatic carbon, oxygen, and antimony being taken as 0·70, 0·74, and 1·41 A., respectively, and the oxygen angle (θ) as 120°, 130°, or 140°, the values calculated for the antimony angle (ϕ) and the angle of fold (ψ) are as follows :

θ	120°	130°	140°
ϕ	88·7	94·2	98·7
ψ	133·0	147·4	168·7

From these figures it appears possible that the angle of fold is in the region of 147°, for an oxygen angle of 130° is probable and the value of 94° for the interbond angle of antimony is not far removed from that found in crystalline antimony and its trihalides. Evidence that the molecule of 10-*p*-carboxyphenyl-2-methylphenoxstibine is, in fact, folded is given in the following description of its resolution into optical enantiomers, though the racemisation of the active acid in boiling alcohol suggests that the folding is considerably less rigid than in the case of the phenoxarsines.

The preparation of phenoxstibines presented some difficulty. At first the synthesis was attempted by the method used by Lesslie and Turner (*J.*, 1934, 1170) for the preparation of phenoxarsines, but the introduction of antimony into 2-amino-4′-methyldiphenyl ether by the Bart–Schmidt process gave yields of only 5—7% of the stibonic acid. The modifications suggested by Morgan (*Proc. Roy. Soc.*, 1930, *A*, **127**, 1; 1933, *A*, **143**, 38) did not improve the yield. Equally low yields of 2-*p*-tolyloxyphenylstibinous chloride were obtained when the diazonium antimony chloride double salt was treated, in dry acetone, with copper powder at — 60° by Nesmejanow's method (*Ber.*, 1929, **62**, 1010) for the introduction of mercury. Cyclisation of the stibonic acid could not be effected by any of the usual reagents and the stibinous chloride was not cyclised by vacuum distillation. Attempts to introduce antimony by modification of the method used successfully for the introduction of tellurium, *i.e.*, the reaction of antimony trichloride on 2-*p*-tolyloxyphenyl mercurichloride, failed.

A synthesis for phenoxstibines was finally achieved by the simultaneous introduction of antimony and ring closure. 2 : 2′-*Dibromo-4-methyldiphenyl ether*, in concentrated ethereal



(I.)

solution, reacted slowly with magnesium turnings, activated by a few drops of methyl iodide, to form a " double " Grignard reagent in about 80% yield. 10-*Phenyl-2-methylphenoxstibine* (I, R = H) was obtained in 35% yield by the reaction of phenylstibinous iodide with this reagent. Unfortunately, oxidation of the methyl group to the carboxyl group wanted for resolution experiments proved impracticable. 10-p-*Cyanophenyl-2-methylphenoxstibine* (I, R = CN) was prepared in a similar way, but the cyanide group could not be hydrolysed to carboxyl without affecting the antimony ring system. 10-p-*Bromophenyl-2-methylphenox-*

stibine (I, R = Br), also obtained in 30—35% yield, could not be induced to form a Grignard reagent. Finally, the reaction of p-*carbethoxyphenylstibinous chloride* with the double Grignard reagent produced the *carbethoxyphenylphenoxstibine* (I, R = CO_2Et), but the yields never exceeded 15%. Hydrolysis of the ester with alcoholic sodium hydroxide gave the acid.

All these phenoxstibines are well-crystallised, stable compounds. The ring system is sensitive to acids, especially when the antimony atom is quinquevalent. For instance, reduction of the stibine dichlorides in acid suspension with sulphur dioxide can result in ring fission or complete elimination of the antimony with the production of phenyl tolyl ether if temperature and sulphur dioxide concentration are not carefully controlled. Alkali, on the other hand, appears to have no effect. The cyanostibine was regained unchanged from fused potassium hydroxide and also after boiling with 30% aqueous or alcoholic sodium hydroxide.

10-p-*Carboxyphenyl-2-methylphenoxstibine* forms salts with all the common alkaloids and with α-phenylethylamine. Strychnine was chosen as the resolving agent because preliminary experiments indicated that the diastereoisomeric salts differed widely in solubility, and the resolution proved comparatively easy when the conditions of preparation and of recrystallisation of the salts were carefully regulated. Prolonged boiling of suspensions of the less soluble diastereoisomeric salt in alcohol resulted in separation of free acid as well as salt, shown by anomalous rotations and the lowering of carbon content on analysis. The difficulty was overcome by dissolving the salt in the minimum volume of boiling chloroform and adding alcohol at 60°. The optically pure *d*-acid strychnine *salt*, $[\alpha]_D$ + 34·5° in chloroform, was very sparingly soluble in alcohol. Purification of the more soluble salt by recrystallisation from boiling alcohol led to second-order asymmetric transformation; in one instance a fraction of salt with $[\alpha]_D$ − 18° was boiled with ethyl alcohol for 30 minutes and an almost equal weight of salt with $[\alpha]_D$ + 17° was regained. In fact unless the fractions of impure *l*-acid strychnine *salt* separating from the original preparation had a specific rotation of − 50° or more, the optically pure material was not obtained. Recrystallisation of fractions of salt with $[\alpha]_D$ − 50° from methyl alcohol raised the rotation to $[\alpha]_D$ − 60·7°. The *acids* regained from the two diastereoisomeric salts had $[\alpha]_D$ + 77·5° and − 77·2° and were stable in chloroform, benzene, and alcohol at room temperature and in the first two solvents at their boiling point, but racemised slowly in boiling alcohol, the specific rotation falling from + 87·64° to + 34·40° after 13 hours' boiling. Solutions of the active acids in 0·1N-sodium hydroxide, -ammonium hydroxide, and -potassium hydrogen carbonate were very faintly opalescent so reliable polarimetric readings could not be taken, but acid regained from the sodium hydroxide solution after one hour's boiling had $[\alpha]_D$ + 55·30°, and that regained from ammonium salt solution which had been kept at room temperature for 14 days had $[\alpha]_D$ + 12·51°.

The comparative ease of racemisation is surprising in view of the pronounced optical stability of the phenoxarsines, although no direct comparison can be made as the phenoxstibine under discussion is not the antimony analogue of any of the known optically active phenoxarsines. Two factors may contribute to the ease of racemisation in this case; first, the larger diameter of the antimony atom may result in an angle of fold closer to 180° and, secondly, the heavy polar *p*-carboxyphenyl group in the 10-position may encourage inversion of the pyramidal configuration of the antimony atom.

Dr. J. Ungar, of the Department of Experimental Medicine, Glaxo Laboratories, Greenford, very kindly undertook to test the *dl*-acid for trypanocidal activity. The compound was tested in aqueous solution (pH 7·8—8·0) by the method described by Goodwin (*J. Pharmacol.*, 1944, **81**, 224). Mice of standard weight (20 g.) were infected with a standard dose of *Trypanosoma equiperdum* and injected intravenously with 0·5 ml. of solutions of *dl*-acid containing 1·0, 0·5, 0·1, or 0·05 mg. of antimony. The peripheral blood of each infected mouse was examined for the presence of trypanosomes at intervals of 24 hours. The results showed that *p*-carboxyphenyl-2-methylphenoxstibine had low toxicity but very little trypanocidal activity compared with "stibophen."

Experimental.

Carbon and hydrogen analyses are by Drs. Weiler and Strauss, Oxford. M. p.'s are uncorrected. Rotations were observed in A.R. chloroform at room temperature in 2-dm. tubes, unless otherwise stated.

2-Bromo-2'-nitro-4-methyldiphenyl Ether.—Half-molar quantities of 3-bromo-*p*-cresol (Zincke and Wiederhold, *Annalen*, 1902, **320**, 203) and *o*-chloronitrobenzene were condensed under the conditions recommended by Henley (*J.*, 1930, 1222). The *ether*, recrystallised from alcohol, separated in thin, hexagonal plates, m. p. 71° (70—75% yield) (Found: Br, 26·0. $C_{13}H_{10}O_3NBr$ requires Br, 25·9%).

2-Bromo-2'-amino-4-methyldiphenyl Ether.—The *amine* (70 g.) was obtained by reduction of the nitro-ether (100 g.) with an equal weight of iron filings and acidified water at 100°. It was extracted

from the iron with boiling alcohol and distilled after removal of the solvent, forming a thick colourless oil, b. p. 180—182°/3 mm., which crystallised, m. p. 45—47° (Found : Br, 28·6. $C_{13}H_{12}ONBr$ requires Br, 28·75%).

2'-Bromo-2-nitro-4-methyldiphenyl Ether.—Chloro-*m*-nitrotoluene was condensed with *o*-bromophenol by Henley's method. Half-molar quantities produced 102 g. of *ether* after recrystallisation from alcohol, from which it separated as pale yellow, rectangular plates, m. p. 70° (Found : Br, 26·2%).

2'-Bromo-2-amino-4-methyldiphenyl Ether.—Reduction of the nitro-ether (100 g.) with an equal weight of iron gave 80 g. of the *amine* (Found : Br, 28·9. $C_{13}H_{12}ONBr$ requires Br, 28·8%), b. p. 188—192°/4 mm., which did not crystallise. Its hydrochloride had m. p. 186—187°.

2 : 2'-Dibromo-4-methyldiphenyl Ether.—The amino-group in each of the foregoing two bases was replaced by bromine by the Sandmeyer, Gattermann, and perbromide procedures. There was no significant difference in the yields from the two, and the perbromide method gave the highest yields when the following conditions were used. The base (55·6 g., 0·2 mol.) was dissolved in 50 c.c. of concentrated hydrochloric acid and 100 c.c. of water, and diazotised with sodium nitrite (14 g.). To the filtered diazonium salt solution, 48 g. (0·3 mol.) of bromine in 140 g. of hydrobomic acid (48%) were added slowly with vigorous stirring. The precipitated perbromide was filtered off, washed well with ice-cold water, and dropped, in small portions, into hot glacial acetic acid. When decomposition was complete the reaction mixture was poured into 2 l. of water, extracted with chloroform, and the extract washed with water and 2N-sodium hydroxide. After removal of the chloroform the residue was distilled at 1 mm. pressure, b. p. 160—200°. Redistillation with a fractionating column gave the *ether* as the main fraction, an almost colourless oil, b. p. 168—171°/0·5 mm. (37·6 g., 55%) (Found : Br, 46·5, 46·8. $C_{13}H_{10}OBr_2$ requires Br, 46·7%).

Preparation of the Grignard Reagent.—Freshly distilled 2 : 2'-dibromo-4-methyldiphenyl ether (17·1 g., 0·05 mol.) was warmed to 30—35° and added slowly to 5·0 g. (0·105 mol.) of magnesium turnings covered with 100 c.c. of dry ether and activated with 3 or 4 drops of methyl iodide. During this addition the flask was kept sufficiently warm to reflux the ether. No obvious reaction occurred until the addition was almost complete. A second portion of 17·1 g. of dibromo-ether in 60 c.c. of ether was added slowly, and the reaction become more vigorous. The whole addition required about 2 hours, and complete solution of the magnesium considerably longer. Reaction was allowed to proceed overnight, the flask being kept warm. The mixture was then cooled to room temperature and filtered from a small quantity of unchanged magnesium into a three-necked flask. The yield of the " double Grignard " reagent was about 80% as shown by decomposition of one batch with dilute acid, pure phenyl *p*-tolyl ether being obtained in 80% yield. The formation of this Grignard reagent presented no difficulty provided the 2 : 2'-dibromo-4-methyldiphenyl ether was freshly distilled, but if it had been kept for 24 hours it reacted very slowly or not at all.

10-Phenyl-2-methylphenoxstibine.—Phenylstibinous iodide (45 g., 0·1 mol.), prepared by Schmidt's method (*Annalen*, 1920, **421**, 218), was dissolved in 400 c.c. of benzene and added slowly to the Grignard reagent from 34·2 g. (0·1 mol.) of dibromo-ether in the 3-necked flask, cooled in a freezing mixture and stirred with a stream of nitrogen. The addition was stopped when the yellow colour of the iodide was no longer discharged, *i.e.*, when 38—40 g. had been added. Most of the ether was removed by distillation, and the residual benzene solution was cooled and treated with ice and dilute hydrochloric acid. The benzene layer was washed with 2N-hydrochloric acid and water. The latter produced a small quantity of finely divided solid which tended to give an emulsion. Distillation of the residue after removal of the benzene gave as the main fraction 32 g. of pale yellow, viscous oil, b. p. 200—210°/0·5 mm. This consisted of the phenoxstibine and polymeric material. As no crystallisation could be induced, the compound was chlorinated in ice-cold carbon tetrachloride (80 c.c.), and the dichloride separated as colourless prisms; recrystallisation from carbon tetrachloride gave 20 g. of *10-phenyl-2-methylphenoxstibine dichloride*, m. p. 112° (decomp.). Recrystallisation from toluene produced long, flat plates, m. p. 104—105°, and from petroleum (b. p. 100—120°) small prisms, m. p. 140—142°. The last is the only solvent from which the compound separates free from solvent of crystallisation (Found : Sb, 26·7; Cl, 15·75. $C_{19}H_{15}OCl_2Sb$ requires Sb, 26·9; Cl, 15·7%).

The dichloride (6 g.) was dissolved in 150 c.c. of absolute alcohol, and ammonia (*d* 0·88) added dropwise until a precipitate of the oxide began to appear. The reaction mixture was heated to b. p., and hydrogen sulphide was passed in until the solution became yellow. On standing in ice, the colour vanished and feathery needles separated. These were recrystallised from light petroleum (b. p. 40—60°) and had m. p. 62—63°, 4 g. The yield of *stibine*, based on the phenylstibinous iodide used, was 30—35% (Found : C, 59·7; H, 4·1. $C_{19}H_{15}OSb$ requires C, 59·9; H, 4·0).

Attempted oxidation of the 2-methyl group to a carboxyl group failed with alkaline or neutral permanganate, dearylation occurring (cf. Schmidt, *Annalen*, 1922, **429**, 141). Acid oxidising agents such as chromic acid in glacial acetic acid resulted in fission of the heterocyclic ring system.

p-Cyanophenylstibinous Chloride and Iodide.—*p*-Aminobenzonitrile was made by reduction of *p*-nitrobenzonitrile with stannous chloride in hydrochloric acid, and the introduction of antimony was effected by Gibson and Kingan's method (B.P. 569,037, 10.6.40). The base (24 g., 0·2 mol.) in 50 c.c. of concentrated hydrochloric acid and 100 c.c. of water was diazotised with 14 g. of sodium nitrite. The filtered solution was added to 30 g. of antimony trioxide in 150 c.c. of concentrated hydrochloric acid at − 5°, and the precipitated double salt filtered off and washed with ice cold alcohol. It was suspended in a mixture of 250 c.c. of 95% alcohol and 50 c.c. of absolute alcohol which had been saturated with hydrogen chloride. Copper bronze (0·5 g.) was added, and the mixture stirred mechanically. Evolution of nitrogen started immediately at 0° but did not become vigorous until the heat of the reaction had raised the temperature to 30°. Decomposition of the double salt was complete within an hour, and on pouring the resultant solution into water the stibonic acid was precipitated in a condition sufficiently pure for the preparation of the stibinous chloride without purification through the ammonium chloride double salt. Reduction was carried out at − 5° in hydrochloric acid with stannous chloride. Since complete drying of the stibonic acid reduced its solubility in hydrochloric acid, and heating,

necessary to obtain solution of the dried acid, resulted in slight decomposition, the reduction was carried out with the freshly precipitated moist acid. Stannous chloride (80 g.) was added in small quantities during ½ hour to a solution of 80 g. of the moist acid in 160 c.c. of hydrochloric acid (*d* 1·126). The stibinous chloride began to separate before the addition of stannous chloride was completed. The reaction mixture was kept in ice for a further 2 hours before filtration. The *chloride* was dried on tile and recrystallised immediately from carbon tetrachloride, from which it separated as colourless needles, m. p. 74—75° (Found: Sb, 41·0. $C_7H_4NCl_2Sb$ requires Sb, 41·2%).

To obtain the *iodide*, the moist acid was dissolved in twice the volume of hydrochloric acid used in the last experiment and reduced in the same way. The stibinous chloride remained in solution, and saturated potassium iodide solution was added till no further precipitation occurred. The bright yellow iodide was filtered off, dried on tile, and immediately recrystallised from carbon tetrachloride; m. p. 98·5—99°, yield 40—50% (Found: Sb, 25·55. $C_7H_4NI_2Sb$ requires Sb, 25·5%).

10-p-*Cyanophenyl*-2-*methylphenoxstibine*.—The preparation of this compound was carried out in the same way as that of the 10-phenyl derivative, 0·05-molar quantities being used. Distillation gave a main fraction of pale yellow, viscous oil (16·9 g.), b. p. 200—240°/0·5 mm. No crystallisation occurred in the original experiment. Chlorination of the oil in carbon tetrachloride at 0° gave the dichloride, m. p. 180—181°, from which the stibine was obtained by hydrogen sulphide reduction in alcoholic ammonia solution. In subsequent preparations the distillate was seeded with the pure stibine which induced partial crystallisation. The crystals were separated from sticky polymeric material with alcohol–light petroleum (b. p. 40—60°) (4 : 1), and when recrystallised from petroleum separated in rosettes of needles, m. p. 82° (7·1 g., 34%) (Found: C, 59·6; H, 3·6; Sb, 30·05. $C_{20}H_{14}ONSb$ requires C, 59·15; H, 3·5; Sb, 30·0%).

Hydrolysis of the *cyanide* was impracticable. Acid hydrolysis eliminated antimony and phenyl *p*-tolyl ether was isolated, and from alkaline hydrolysis the unchanged cyanide was regained. The compound is exceptionally stable to alkali; 1 g. was held for 15 minutes in 5 g. of molten potassium hydroxide and was regained unchanged.

10-p-*Bromophenyl*-2-*methylphenoxstibine*.—*p*-Bromoaniline was converted into *p*-bromophenylstibinous iodide by the method described for the *p*-cyano-compound and obtained in 35—40% yield, m. p. 122—123° (cf. Blicke and Oakdale, *J. Amer. Chem. Soc.*, 1933, **55**, 1198). The cyclic stibine was prepared by the method described above, using 0·05-molar quantities. Distillation of the reaction product gave a very viscous, pale yellow oil, b. p. 220—260°/0·3 mm. (18·4 g.). Chlorination of this in ice-cold carbon tetrachloride solution produced 13·7 g. of dichloride, m. p. 202°, from which the stibine was obtained by reduction with hydrogen sulphide in alcoholic ammonia solution. The pure stibine was used to seed the distillate from further preparations and partial crystallisation occurred. The crystals were separated from by-products with alcohol–light petroleum (b. p. 60—80°) (4 : 1) and recrystallised from alcohol. The *stibine* is sparingly soluble in alcohol and separates from it in rosettes of colourless needles, m. p. 116° (yield 30—35%) (Found: C, 49·7; H, 3·1; Sb, 26·4. $C_{19}H_{14}OBrSb$ requires C, 49·6; H, 3·1; Sb, 26·5%). An ethereal solution of the bromostibine was added to magnesium turnings activated by iodine or by methyl iodide, but no formation of a Grignard reagent could be induced.

p-*Carbethoxyphenylstibinous Chloride*.—When ethyl *p*-aminobenzoate was converted into the corresponding stibonic acid by the usual Bart–Schmidt reaction, the ester group was partially hydrolysed (cf. Clark, *J.*, 1932, 1826). The carboxyl group was re-esterified by suspending the acid (10 g.) in absolute alcohol (50 c.c.), passing in hydrogen chloride till solution was complete, and then boiling the solution under reflux for an hour. *p*-Carbethoxyphenylstibonic acid was precipitated on pouring the alcoholic solution into water. When antimony was introduced by Gibson and Kingan's method (*loc. cit.*) no hydrolysis of the ester group occurred and a yield of 50—55% of the stibonic acid was obtained after purification through the ammonium chloride double salt.

Reduction.—When the stibonic acid (40 g., moist) was dissolved in hydrochloric acid (60 c.c., *d* 1·126), the tetrachloride separated as a viscous oily layer and satisfactory reduction could only be obtained if the reaction mixture, kept below 0°, was shaken vigorously after each addition of stannous chloride, 40 g. in all being required. The *dichloride* was filtered off after standing for 2 hours at 0°, dried on tile, and recrystallised from carbon tetrachloride, in which it is rather insoluble, or from ethylene dichloride. It separated from the latter in flat elongated plates, m. p. 127°, and was highly sternutatory (Found: Sb, 35·5. $C_9H_9O_2Cl_2Sb$ requires Sb, 35·7%).

Preparation of the stibinous iodide by the method used previously was impracticable because of the very low solubility of the stibinous chloride in hydrochloric acid. Attempts to prepare the iodide by solution of the pure chloride in dry acetone and addition of the calculated quantity of sodium iodide in the same solvent, followed by removal of the precipitated sodium chloride and evaporation of the solvent under reduced pressure, afforded an *iodide* which was very insoluble in organic solvents, except alcohol and ethyl acetate from which it did not crystallise. Small quantities obtained in crystalline form melted indefinitely and showed a deficit of antimony (Found: Sb, 22·4, 22·3. $C_9H_9O_2I_2Sb$ requires Sb, 23·2%). The stibinous chloride was therefore used in the reaction with the Grignard reagent. It has distinct disadvantages because of rather low solubility and because completion of the reaction could not be seen, as in previous experiments, by discharge of the yellow colour of the iodide.

10-p-*Carbethoxyphenyl*-2-*methylphenoxstibine*.—The Grignard reagent prepared from 17·1 g. (0·05 mol.) of dibromo-ether was filtered into a three-necked flask, diluted with ether to 250 c.c., cooled in a freezing mixture, and stirred with a stream of nitrogen while a solution of *p*-carbethoxyphenylstibinous chloride (14 g., 0·04 mol.) in 250 c.c. of dioxan was added during 15—20 minutes. A thick, cream-coloured mass was precipitated. The mixture was allowed to reach room temperature and boiled under reflux for 1 hour, during which the precipitate became much more crystalline; it was then cooled in a freezing mixture and treated with ice and dilute hydrochloric acid. The addition of acid produced an orange-red colour which was partly removed on washing the ethereal layer with water to remove dioxan. Emulsions were frequent at this stage owing to separation of small quantities of water and ether-

insoluble material. The reddish-brown glass obtained after the removal of ether could not be distilled without decomposition at 0·25 mm. pressure, but the stibine was obtained from it by repeated extraction with light petroleum (b. p. 40—60°). A simpler method of isolation was to distil off ether until about 40—50 c.c. remained, and allow the stibine to crystallise from this. The *stibine*, recrystallised from alcohol, separated in flat needles, m. p. 136—137° (2·0 g., 15%) (Found: C, 58·2; H, 4·3; Sb, 26·8. $C_{22}H_{19}O_3Sb$ requires C, 58·3; H, 4·2; Sb, 26·9%).

10-p-*Carboxyphenyl-2-methylphenoxstibine*.—The ester (5 g.) was dissolved in 100 c.c. of 5% alcoholic potassium hydroxide and boiled under reflux for ½ hour. The solution was poured into 500 c.c. of water and acidified with dilute hydrochloric acid. The precipitated *acid* was filtered off, dried, and recrystallised from alcohol, separating in rosettes of small needles (4·1 g.), m. p. 201° (Found: C, 56·5; H, 3·6; Sb, 28·8. $C_{20}H_{15}O_3Sb$ requires C, 56·5; H, 3·6; Sb, 28·65%).

Resolution with Strychnine.—Several experiments on the resolution of the *dl*-acid with strychnine were carried out, including one method of partial precipitation. All of these permitted the isolation of pure *d*-acid strychnine salt but most failed to produce the *l*-acid salt in a state of optical purity. Unfortunately, neither the cinchonine nor the cinchonidine salt possessed the reverse solubility relationship, so it was impossible to complete the resolution by their use, and brucine proved of no value as a resolving agent because the salts always separated initially as an oil. Quinine gave an apparently incomplete resolution, the significance of which remains doubtful and which will be further investigated. Finally, a complete resolution was obtained with strychnine as follows.

The *dl*-acid (5·25 g.) and strychnine (4·13 g.) were dissolved respectively in 300 c.c. of warm alcohol and 50 c.c. of chloroform, and the solutions mixed. The first fraction, F1 (5·0 g.), had $[\alpha]_D$ + 17·0° (*c*, 0·501). On removal of the chloroform under vacuum below 25°, F2 (2·3 g.) separated, $[\alpha]_D$ − 59·11° (*c*, 0·515). F3 (1·4 g.,), $[\alpha]_D$ − 41·10° (*c*, 0·510), separated when the mother-liquor was concentrated to 150 c.c. by distillation at 12 mm., and further concentration to 50 c.c. gave, on standing, F4 (0·6 g.), $[\alpha]_D$ − 19·96° (*c*, 0·501). F4 is apparently the *dl*-acid strychnine salt, as a solution of equivalent quantities of the acid and strychnine in chloroform had $[\alpha]_D$ − 19·97° (*c*, 0·545). Three recrystallisations of F1 from alcohol–chloroform gave 2·3 g. of *d*-acid strychnine *salt*, $[\alpha]_D$ + 34·4° (*c*, 0·510), as very small needles, m. p. 218° (Found: C, 64·0; H, 5·0. $C_{41}H_{37}O_5N_2Sb$ requires C, 64·9; H, 4·9%).

F2 after two recrystallisations from methyl alcohol had $[\alpha]_D$ − 60·73° (*c*, 0·510), 1·6 g., which separated as long thin needles, m. p. 100° (decomp.) (Found: C, 63·0; H, 5·0. $C_{41}H_{37}O_5N_2Sb,H_2O$ requires C, 63·3; H, 5·05%). All these salts were optically stable in chloroform solution at room temperature. Prolonged boiling of solutions of the *l*-acid strychnine *salt* in ethyl alcohol during recrystallisation had to be avoided because the resulting salt became less lævorotatory. To obtain evidence of this second-order asymmetric transformation, 0·6 g. of salt with $[\alpha]_D$ − 18·0° was boiled with 20 c.c. of absolute alcohol for 30 minutes, the salt insoluble in this volume was filtered off, and the filtrate allowed to crystallise. The undissolved salt (0·1 g.) had $[\alpha]_D$ + 18·5°, and the salt separating from the filtrate (0·45 g.) had $[\alpha]_D$ + 17·0°. Optically pure *l*-acid strychnine salt was never obtained unless the fraction separating in the original preparation of the salt had approximately $[\alpha]_D$ − 50°, and purification had to be done by quick recrystallisation from the minimum volume of methyl alcohol.

d-10-p-*Carboxyphenyl-2-methylphenoxstibine*.—The *d*-acid was obtained by extraction of a chloroform solution of its strychnine salt with 0·5N-hydrochloric acid and removal of the chloroform under reduced pressure. It had $[\alpha]_D$ + 77·50° in chloroform (*c*, 0·555), $[\alpha]_D$ + 89·6° in benzene (*c*, 0·513), and $[\alpha]_D$ + 87·64° in absolute alcohol (*c*, 0·291). No change in rotation occurred when a solution of the active acid in chloroform was kept for 14 days at room temperature, or at 45° for 4 hours, or boiled under reflux for 2 hours. A solution of the acid in benzene was boiled for 1 hour and no change was noticeable. In alcohol, on the other hand, the rotation of the acid decreased on boiling the solution and the following results were obtained (initial rotation, $[\alpha]_D$ + 87·64°):

Time of boiling (hrs.)	1	2	3	5	8	13
$[\alpha]_D$	+77·30°	+68·73°	+61·73°	+53·26°	+46·40°	+34·35°

Change in concentration of the solution occurs by evaporation, so the racemisation does not appear to obey the unimolecular law. Acid recovered from such racemisation experiments was chemically pure (Found: C, 56·3, H, 3·7%). Recrystallisation of the active acid from methyl alcohol was possible without much racemisation; the first fraction to separate had $[\alpha]_D$ + 77·3° but the second had $[\alpha]_D$ + 64·4°. The optically pure *acid* melts at 192° (bath preheated to 180°) (Found: C, 56·65; H, 3·7. $C_{20}H_{15}O_3Sb$ requires C, 56·5, H, 3·6%).

l-10-p-*Carboxyphenyl-2-methylphenoxstibine*.—The l-*isomer* was obtained from the more soluble strychnine salt in a similar manner and had $[\alpha]_D$ − 77·2° (*c*, 0·518; chloroform) and − 89·9° (*c*, 0·250; benzene), m. p. 192° (preheated bath) (Found: C, 56·7; H, 3·7%).

Both active acids on solution in dilute alkali (0·05N-NaOH, 0·1N-NH_4OH, and 0·1N-$KHCO_3$) gave solutions which were faintly opalescent. It was impossible to obtain reliable polarimetric readings, but the specific rotations of these solutions appeared to be slightly greater than that of the pure acid in chloroform; *e.g.*, $[\alpha]_D$ + 77·9° in 0·05N-NaOH. This solution was boiled for an hour and the acid regained from it had $[\alpha]_D$ + 55·9°. The ammonium salt was kept at room temperature for 14 days and the acid regenerated from it had $[\alpha]_D$ + 12·5°.

Racemisation apparently occurs on heating in the absence of solvents because the m. p.'s of the active acids ranged from 194° to 198° when observed in a bath heated slowly from room temperature. In a bath pre-heated to 180°, they melted sharply at 192°. The following m. p.'s were obtained with mixtures of the *d*- and the *dl*-acid. The mixtures (inserted at 180°), with the exception of the 50 : 50 mixture, melted over a range of 2—3° and the m. p. given is that of complete fusion.

d-Acid, %	100	90·0	83·3	75·0	66·6	50·0
M. p.	192°	187°	191°	194°	196·5°	201°

The author thanks the Chemical Society and Imperial Chemical Industries Ltd. for grants which defrayed the costs of chemicals and microanalyses respectively. For the tests on trypanocidal activity the author is greatly indebted to Dr. Ungar, of the Department of Experimental Medicine, Glaxo Laboratories, Greenford, Middlesex.

UNIVERSITY COLLEGE, SOUTHAMPTON. [*Received, April 15th*, 1946.]

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3. *The Action of Acidic Reagents on Ethylene Oxide Anhydro Sugars. Part I. The Action of Acid Reagents on* 4 : 6-*Benzylidene* 2 : 3-*Anhydro* α-*Methylalloside.*

By F. H. NEWTH, W. G. OVEREND, and L. F. WIGGINS.

The action of hydrochloric and hydrobromic acids on 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside has been studied, and each reagent has been found to produce two distinct halogeno α-methylhexosides. Hydrobromic acid gave 2-bromo α-methylaltroside and 3-bromo α-methylglucoside; hydrochloric acid gave 2-chloro α-methylaltroside and 3-chloro α-methylglucoside. The constitution of each of these substances has been established.

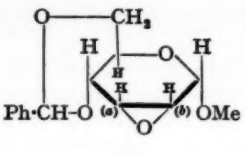
It has been observed that by the action of acid reagents on the 2 : 3-anhydro alloside the main product is a glucose derivative, whereas it has been shown previously that, by the action of alkaline reagents on the same anhydro sugar, the main product is an altrose derivative. Experiments using sulphuric and oxalic acids as the acidic reagents on the 2 : 3-anhydro alloside have shown that these substances produce a similar effect to that of the halogen acids.

EXTENSIVE work has been done in the past on the scission of ethylene oxide anhydro rings with alkaline reagents. Thus, Peat and Wiggins (*J.*, 1938, 1810) studied the behaviour of 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside (I) towards alkaline reagents and discovered that two products were formed, namely, a derivative of glucose and a derivative of altrose with the latter predominating. When ammonia was the effective reagent 2-amino 4 : 6-benzylidene α-methylaltroside (II) was obtained in 80% yield accompanied by 3-amino 4 : 6-benzylidene α-methylglucoside (III) in 10% yield, both compounds being isolated as their acetates. Similarly, Richtmyer and Hudson (*J. Amer. Chem. Soc.*, 1941, **63**, 1727) obtained 4 : 6-benzylidene α-methylaltroside and 4 : 6-benzylidene α-methylglucoside in 84% and 7% yield respectively by the action of potassium hydroxide on the alloside (I).

Again, in the ring scission of 4 : 6-benzylidene 2 : 3-anhydro β-methyltaloside (IV) with sodium methoxide (Wiggins, *J.*, 1944, 522) two products were obtained, which were 4 : 6-benzylidene 3-methyl β-methylidoside (V) and 4 : 6-benzylidene 2-methyl β-methylgalactoside (VI), with the former largely in excess. It will be observed that Walden inversion is concomitant with ring scission and accompanies the scission in both directions.

It is of interest that in the anhydro taloside (IV) it is the bond (*c*) furthest from the glycosidic group that breaks to the largest extent, giving rise to a derivative of idose, whereas in the alloside (I) it is the bond (*b*) nearest to the glycosidic group that predominantly breaks. Ring scission of 4 : 6-benzylidene 2 : 3-anhydro α-methylmannoside (VII) with sodium methoxide (Robertson and Griffith, *J.*, 1935, 1193) proceeds in accordance with the above observations, since the main product is 4 : 6-benzylidene 3-methyl α-methylaltroside (VIII).

It appears therefore that, in the ring opening of 2 : 3-ethylene oxide anhydro rings, if the ring lies above the plane of the sugar ring then the C–O bond furthest from the glycosidic group suffers the most extensive scission, whereas if the anhydro ring lies below the plane of the sugar ring, then it is the C–O bond nearest to the glycosidic group which breaks to the greater extent. Although these facts seem to hold for all cases of the ring scission of 2 : 3-anhydro methylhexosides so far studied, ring opening seems to proceed in the opposite sense when the reaction is applied to ethylene oxide derivatives of 1 : 6-anhydro sugars. This statement, however, is based only on the one example as yet available. James, Stacey, Smith, and Wiggins (*Nature*, 1945, **156**, 308; *J.*, 1946, 625) in their constitutional synthesis of chondrosamine found that ring fission of 2 : 3-1 : 6-dianhydro β-talose (IX) led mainly, not to an idose derivative (X) which would have been expected had the ring scission proceeded in the same way as with 4 : 6-benzylidene 2 : 3-anhydro β-methyltaloside, but to a derivative of galactose (XI). That is to say, instead of the C–O bond (*e*) breaking to the largest extent, it is bond (*f*) that suffers the greatest rupture. Thus the presence of the 1 : 6-anhydro ring alters the balance of isomers produced on ethylene oxide ring scission. We have now found that acidic reagents have a similar effect, at least in the one case examined, that of 2 : 3-anhydro α-methylalloside (I). Thus with alkaline reagents the C–O bond (*a*) nearest the glycosidic group predominantly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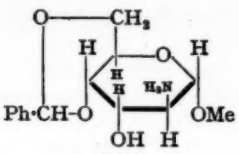
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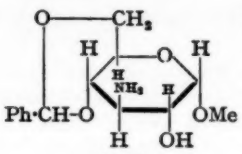
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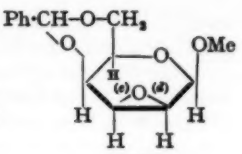
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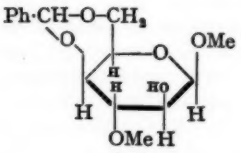
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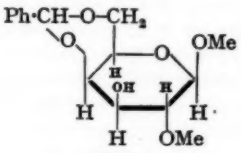
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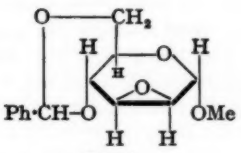
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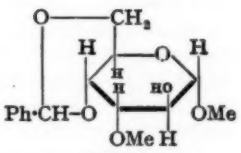
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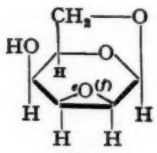
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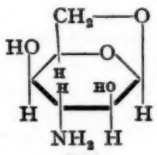
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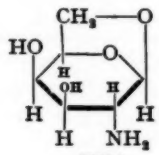
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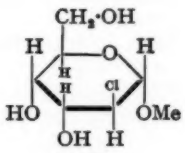
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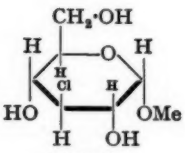
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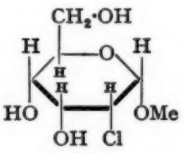
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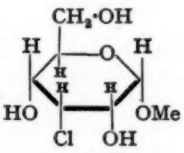
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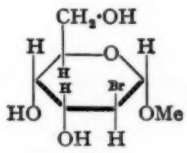
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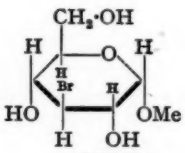
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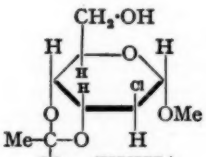
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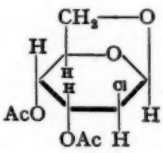
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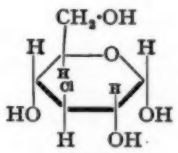
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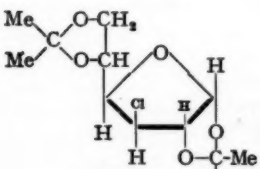
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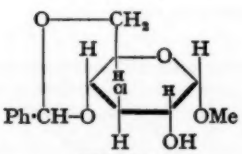
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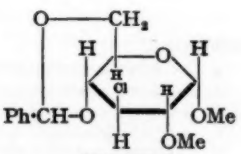
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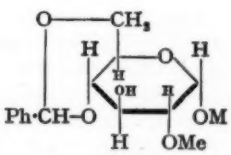
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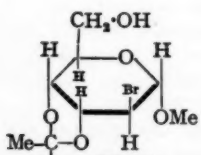
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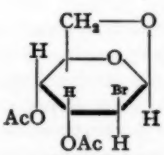
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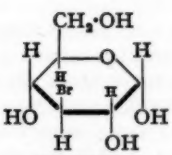
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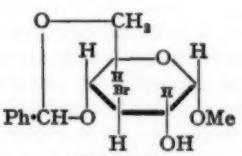
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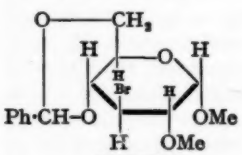
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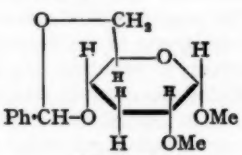
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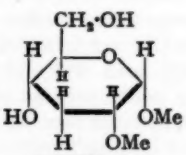
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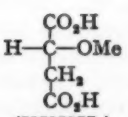
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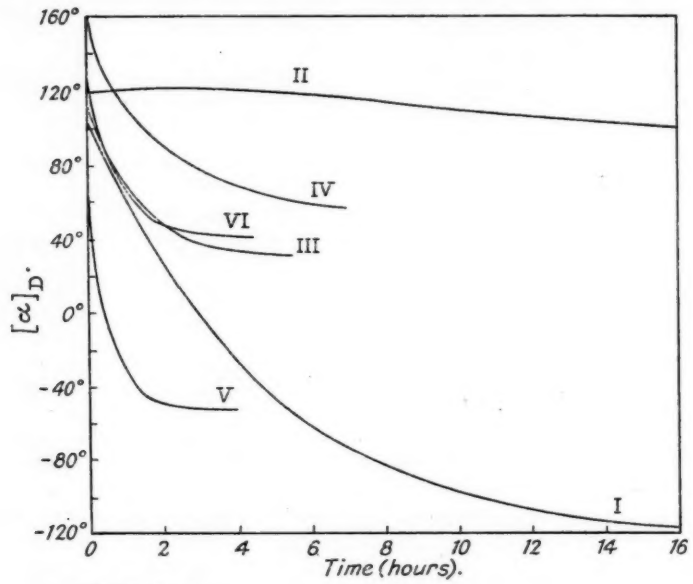
breaks, but when acids are used the bond (*b*) furthest from the glycosidic group is ruptured to a greater extent than (*a*).

The alloside (I) on treatment with hydrochloric acid gives two isomers, **2-*chloro* α-*methyl-altroside*** (XII) and **3-*chloro* α-*methylglucoside*** (XIII), with the latter predominating, although the difference in the amounts of the two isomers is not so pronounced as that observed when alkaline reagents were used to effect ring scission. Similarly, the products obtained by the action of hydrobromic acid were the corresponding bromo derivatives, **3-*bromo* α-*methylglucoside*** (XVII) and **2-*bromo* α-*methylaltroside*** (XVI), the former being produced to the greater extent.

The chloro hexosides, produced by the action of hydrochloric acid in acetone solution on 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside, were first encountered by Robertson and Dunlop (*J.*, 1938, 472) who did not, however, establish their constitution. The bromo hexosides obtained in the course of this investigation have not been previously described. We have now collected evidence enabling us to state with confidence the structure of these four halohydrins.

When the ethylene oxide ring of the alloside (I) is opened with hydrochloric acid, the formation of four isomeric chlorohydrins (XII, XIII, XIV, and XV) is possible.



Hydrolysis of:

I. **2-*Chloro* α-*methylaltroside* with 5% *sulphuric acid.***
II. **3-*Chloro* α-*methylglucoside* with 15% *sulphuric acid.***
III. **3-*Chloro* α-*methylglucoside* with 25% *sulphuric acid.***
IV. **α-*Methylglucoside* with 10% *sulphuric acid.***
V. **2-*Bromo* α-*methylaltroside* with 5% *sulphuric acid.***
VI. **3-*Bromo* α-*methylglucoside* with 25% *sulphuric acid.***

Robertson and Dunlop (*loc. cit.*) found that each of the two chloro compounds isolated was reconverted into the original anhydro sugar by moist silver oxide. Therefore, (XIV) and (XV) are eliminated as possible structures, since we know that anhydro ring formation does not take place unless accompanied by Walden inversion (see Peat, *Ann. Reports*, **1939**, **36**, 258).

The two chloro α-methylhexosides must therefore be derivatives of altrose and glucose and may be represented as (XII) and (XIII), the problem being to assign the correct configuration to the two isomers. The solution of this question has been provided by experiments on the hydrolysis of the chloro α-methylhexosides. The products of the reaction of hydrochloric acid with the anhydro alloside (I), which we shall designate as fraction (I) and fraction (II), were obtained in yields of 20% and 40% respectively. Fraction (I) hydrolysed readily with N-sulphuric acid, a change which was accompanied by a rapid and marked alteration in the specific rotation of the compound (see figure). On completion of the hydrolysis the solution was only faintly reducing to Fehling's solution, and a liquid was isolated which after acetylation gave a non-reducing crystalline compound having a very high negative rotation ($[\alpha]_D$ — 212·2°).

This behaviour was strikingly reminiscent of that of crystalline altrose (Hudson and Richtmyer, *J. Amer. Chem. Soc.*, 1935, **57**, 1716; 1940, **62**, 961). The specific rotation of altrose when treated with hot acid solution changes from $[\alpha]_D + 34°$ to $- 98°$, a change which is accompanied by partial loss in reducing power, this behaviour being ascribed to the formation of 1 : 6-anhydro β-altrose (altrosan). The similarity between these observations and the behaviour of the chloro sugar of fraction (I) was so close as to suggest that, since either fraction (I) or (II) must have the altrose configuration, it must be fraction (I) which did in fact possess this constitution. Further evidence in support of this came from its condensation with acetone. Of the two possible formulæ (XII) and (XIII), clearly only *2-chloro α-methylaltroside* (XII) could form an acetone compound. Condensation of fraction (I) with acetone gave a monoacetone compound which must therefore be *2-chloro* 3 : 4-*monoacetone α-methylaltroside* (XVIII), and the derivative of altrosan produced by the acid hydrolysis of fraction (I) was *2-chloro* 3 : 4-*diacetyl* 1 : 6-*anhydro* β-*altrose* (XIX). Since we have shown the constitution of fraction (I) to be that of 2-chloro α-methylaltroside, it follows that the second isomer, fraction (II), must possess the only other possible structure, that of 3-chloro α-methylglucoside (XIII). This substance was extremely difficult to hydrolyse by acid, requiring 25% sulphuric acid to effect hydrolysis at a reasonable rate (see figure, in which the hydrolysis of α-methylglucoside is shown for comparison). Here the change in rotation was less marked ($[\alpha]_D + 135 \longrightarrow + 30°$) than in the case of fraction (I), and the crystalline product isolated, which strongly reduced Fehling's solution, was *3-chloro glucose* (XX). This condensed with acetone to yield a diacetone derivative which would appear to be *3-chloro* 1 : 2-5 : 6-*diacetone glucofuranose* (XXI). The fact that the chloro sugar does condense with acetone to give a diacetone compound is additional proof of its constitution since atomic models show that 3-chloro glucose, but not 2-chloro altrose, could form a diacetone compound.

Only 3-chloro α-methylglucoside forms a crystalline benzylidene compound, 3-chloro 4 : 6-benzylidene α-methylglucoside (XXII), a compound which by treatment with sodium methoxide can be transformed into the original 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside. The 2-chloro α-methylaltroside gave only a syrupy benzylidene compound, together with some of the original anhydro alloside (I) which had been produced undoubtedly by the action of the sodium carbonate, used in the isolation process, on the syrupy 2-chloro benzylidene α-methylaltroside. The 3-chloro 4 : 6-benzylidene α-methylglucoside (XXII) was easily converted into *3-chloro* 4 : 6-*benzylidene* 2-*methyl α-methylglucoside* (XXIII), but attempts to remove the halogen atom either by hydrogenation or by alkaline hydrolysis failed. Had the hydrolysis been successful, 4 : 6-benzylidene 2-methyl α-methylglucoside (XXIV) would have been formed. However, the behaviour of this compound was in accordance with our experiences with tosyl esters of sugar derivatives in which anhydro ring formation is not possible, for only when such ring formation can occur does the hydrolysis of tosyl ester occur readily.

On treating 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside with hydrobromic acid in aqueous acetone solution, a mixture of two bromo α-methylhexosides was formed; fraction (A), m. p. 153°, $[\alpha]_D + 86{\cdot}2$, was shown to be 2-bromo α-methylaltroside, and fraction (B), m. p. 132—133°, $[\alpha]_D + 109{\cdot}8$, was 3-bromo α-methylglucoside. (A) was obtained in 10% and (B) in 40% yield, amounts which are similar to those of the corresponding chloro sugars obtained above. That is to say there has been again a reversal of the balance of the isomers produced by the action of the acid on the anhydro compound when compared with that produced when alkaline reagents were the agents causing ring scission.

The structure of the two bromo α-methylhexosides has been established as follows. The formation of four isomers, analogous to those mentioned in the discussion of the chloro α-methylhexosides, is theoretically possible on ring scission of the alloside with hydrobromic acid. The 2-bromo and 3-bromo derivatives of allose are eliminated by virtue of the fact that fraction (A) and fraction (B) have both been converted into the original 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside, so that we are again left with the problem of the allocation of the correct configuration, namely, that of 2-bromo α-methylaltroside (XIV) and 3-bromo α-methylglucoside (XV) to fraction (A) and (B). The problem would be solved if the constitution of one only of the isomers could be established, and this we have been able to do unequivocally by the conversion of one of the isomers into a compound of known constitution.

Fraction (B) was converted into crystalline *3-bromo* 4 : 6-*benzylidene α-methylglucoside* (XXVIII) which on methylation with methyl iodide and silver oxide gave *3-bromo* 4 : 6-*benzylidene* 2-*methyl α-methylglucoside* (XXIX). This, on catalytic hydrogenation over Raney nickel in the presence of alcoholic potash, gave 4 : 6-benzylidene 2-methyl 3-deoxy-α-methylglucoside (XXX) identical with the product obtained by Prins (*Helv. Chim. Acta*, 1946, **29**, 1)

from the hydrogenation products of 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside. Prins proved the constitution of (XXX) by hydrolysis to 2-methyl 3-deoxy-α-methylglucoside (XXXI) followed by oxidation to *d*-methoxysuccinic acid (XXXII), which could only be obtained from a compound having the constitution (XXXI). It is clear, therefore, that fraction (B) must be 3-bromo α-methylglucoside (XV) and consequently fraction (A) must possess the only alternative structure, that of 2-bromo α-methylaltroside (XIV).

Additional evidence in support of this contention comes from experiments on the hydrolysis of the two isomers. Fraction (A) undergoes hydrolysis easily with alteration in specific rotation from $[\alpha]_D + 87°$ to $[\alpha]_D - 90°$ (see figure), a change reminiscent of the behaviour of altrose derivatives (Richtmyer and Hudson, *loc. cit.*). The product, which only faintly reduced Fehling's solution, gave on acetylation a liquid product, which probably contained 2-bromo 3 : 4-diacetyl 1 : 6-anhydro β-altrose (XXVI). Moreover, fraction (A) condensed with acetone to yield a crystalline monoacetone compound, and, since only 2-bromo α-methylaltroside could do this, the compound must be 2-*bromo* 3 : 4-*monoacetone* α-*methylaltroside* (XXV). Fraction (B) failed to condense with acetone.

The hydrolysis of fraction (B) took place with difficulty, requiring 25% sulphuric acid to effect a fairly rapid rate of reaction; in this behaviour it was very similar to 3-chloro α-methylglucoside (see figure). The product, which was strongly reducing to Fehling's solution, was isolated as a crystalline bromo sugar, which must be 3-*bromo glucose* (XXVII).

It is clear, therefore, that the ring scission of 2 : 3-anhydro α-methylalloside with hydrobromic and hydrochloric acids follows the same course as when alkaline agents are used to effect ring opening, except that the respective yields of the two isomeric sugar products are reversed. The ring scission with each of the acid agents used is accompanied by a small amount of a third component (not a simple halogeno methylhexoside) which as yet we have not identified, but on which further work is being carried out.

We have used two other acidic reagents, namely, oxalic and sulphuric acids, to effect anhydro ring scission, though with less definite results than those obtained with the halogen acids. Sulphuric acid, after removing the benzylidene residue from 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside, effected partial ring opening giving rise to α-methylglucoside in 15% yield. No other substance, except unchanged 2 : 3-anhydro alloside, isolated as its benzylidene derivative, could, however, be isolated. The fact that α-methylglucoside and not α-methylaltroside is obtained does suggest, however, that sulphuric acid acts in the same way as the halogen acids. In addition, a compound, similar to the third component of the products of the action of halogen acids on the alloside (I), was also isolated by ether extraction of the reaction mixture, but has not yet been identified

During experiments, designed merely to remove the benzylidene residue from 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside, we found that oxalic acid is also effective in opening this particular anhydro ring, the effect being similar to sulphuric acid in so far as we could only isolate α-methylglucoside, in addition to the 2 : 3-anhydro α-methylalloside which remained intact.

Experimental.

Action of Hydrochloric Acid on 4 : 6-*Benzylidene* 2 : 3-*Anhydro* α-*Methylalloside.*—The alloside (12·5 g., prepared according to the method of Richtmyer and Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1727) was dissolved in acetone (1 l.) and hydrochloric acid (36 c.c., 2N) added. The solution was boiled under reflux for 4 hours. The acid was neutralised with lead carbonate and the solution filtered. The precipitate was washed with acetone, the combined filtrate and washings were evaporated until free from acetone, and the aqueous solution (A) was extracted with ether to remove benzaldehyde. On evaporation of the ether and subsequent distillation of the benzaldehyde in steam, a syrup remained after evaporation of the water. This was dissolved in ether, evaporation of which gave a low-melting, crystalline substance. It was recrystallised with some difficulty from ether–light petroleum in large prisms, m. p. 59°, $[\alpha]_D^{18°} + 66·2°$ in chloroform (*c*, 1·630). This compound has so far not been identified.

The aqueous solution (A), after ether extraction, was evaporated to dryness under diminished pressure and the residue extracted with boiling ethyl acetate. This extract on being evaporated gave a crystalline solid (8·5 g.). On fractional recrystallisation from ethyl acetate, two fractions were obtained. Fraction (I) had m. p. 160—161°, $[\alpha]_D^{20°} + 111·0°$ in methyl alcohol (*c*, 1·960). Yield, 1·6 g. (Found: C, 40·0; H, 6·1. $C_7H_{13}O_5Cl$ requires C, 39·7; H, 6·1%). Fraction (II) had m. p. 136—138°, $[\alpha]_D^{20°} + 158·5°$ in methyl alcohol (*c*, 0·98). Yield, 2·0 g. (Found: C, 40·1; H, 6·6. $C_7H_{13}O_5Cl$ requires C, 39·7; H, 6·1%). For these two isomeric chloro α-methylhexosides, which are subsequently shown to be 2-*chloro* α-*methylaltroside* and 3-*chloro* α-*methylglucoside* respectively, Robertson and Dunlop (*loc. cit.*) give m. p. 160—162°, $[\alpha]_D^{15°} + 113·1°$ in methyl alcohol, and m. p. 136—138°, $[\alpha]_D^{15°} + 157·2°$ in methyl alcohol.

The syrupy residue which could not be crystallised further was shaken with benzaldehyde (10 c.c.) and zinc chloride (1·5 g.) for 24 hours. The solution was then poured into a mixture of petrol and water, whereupon a crystalline precipitate separated. This crystallised from alcohol in needles, m. p. 165°,

$[\alpha]_D^{20°}$ + 50·9° in chloroform (*c*, 1·37). Yield, 2·5 g. (Found: C, 56·1; H, 6·1; Cl, 12·2. $C_{14}H_{17}O_6Cl$ requires C, 56·0; H, 5·7; Cl, 11·7%).

Condensation of Fraction (II) with Benzaldehyde.—The substance (4·0 g.) was shaken for 24 hours with benzaldehyde (15 c.c.) and zinc chloride (2 g.). The solution was poured into a mixture of petrol and water and the crystalline precipitate which separated recrystallised from alcohol; m. p. 165° (3·2 g.). The benzylidene compound obtained above was therefore the same as that of fraction (II) and was a chloro benzylidene α-methylhexoside, shown to be 3-*chloro* 4 : 6-*benzylidene α-methylglucoside*.

The yield of fraction (I) was 18·3% and that of fraction (II) (including the part isolated as the benzylidene derivative) was 38·5%.

In a second experiment, the alloside (13 g.) was dissolved in acetone (1 l.) containing hydrochloric acid (26 c.c., 2N) and the solution heated under reflux for 5½ hours. The acid was then neutralised with lead carbonate, and the precipitate collected and washed with acetone. The combined filtrate and washings were evaporated until free from acetone and the aqueous solution was extracted with ether to remove benzaldehyde. In this experiment, this extract was neglected. The aqueous layer was evaporated to dryness, and the residue extracted with boiling ethyl acetate. This extract deposited crystals.

Fraction (I), m. p. 156—160°, on being recrystallised had m. p. 161° (1·93 g.). The mother liquors were evaporated to dryness and the residue recrystallised from ethyl acetate giving fraction (II), m. p. 136—138° (3·1 g.). A small amount of fraction (I) next separated m. p. 161° (0·55 g.). Total yield of fraction (I) was 2·48 g. The syrupy mother liquors were evaporated to dryness and the residual syrup (2·45 g.) benzylidenated in the manner described above. The crystalline benzylidene compound of fraction (II) was obtained, m. p. 165° [0·95 g. which corresponds to 0·67 g. of fraction (II) itself].

Fraction (I) was obtained in a yield of 23·6%, and fraction (II) (including that obtained as the benzylidene derivative) in a yield of 36%.

Condensation of Fraction (I) with Acetone.—The compound (0·6 g.) was shaken with dry acetone (25 c.c.) containing concentrated sulphuric acid (0·15 c.c.). Solution was complete within one hour. After 24 hours, the solution was neutralised by anhydrous sodium carbonate, the solution filtered, and the residue washed with acetone. The combined filtrate and washings were evaporated, giving a thick colourless liquid (0·66 g.) which slowly crystallised. It crystallised from ethyl acetate–light petroleum in prisms, m. p. 60°, $[\alpha]_D^{20°}$ + 75·9° in chloroform (*c*, 0·80). It was 2-*chloro* 3 : 4-*monoacetone α-methylaltroside* (Found: C, 47·2; H, 6·8; Cl, 14·7. $C_{10}H_{17}O_6Cl$ requires C, 47·6; H, 6·7; Cl, 14·1%).

Attempted Condensation of Fraction (II) with Acetone.—The crystalline substance, m. p. 136—138° (1 g.), was shaken with acetone (25 c.c.) containing concentrated sulphuric acid (0·5 g.) for 24 hours. The crystals rapidly dissolved. The acid was neutralised with anhydrous sodium carbonate, the solution filtered, and the inorganic residue washed with acetone. The combined filtrate and washings were evaporated in the presence of a trace of barium carbonate and the residue, which rapidly crystallised, was recrystallised from ethyl acetate; m. p. 136—137° (0·7 g.). It was unchanged starting material (mixed m. p.). This experiment indicated that fraction (II) could not form an acetone compound.

Hydrolysis of 2-Chloro α-Methylaltroside [Fraction (I)] with Sulphuric Acid.—The substance (0·73 g.) was dissolved in sulphuric acid (30 c.c., 0·1N) (*c*, 2·44) and heated at 100°: $[\alpha]_D$ + 14·7° (initial value); + 111·5° (30 mins.); + 109·0° (90 mins.). The reaction was proceeding very slowly, so the strength of the acid was increased tenfold (*c*, 2·38) and the heating continued until constant rotation was reached: $[\alpha]_D$ + 105·1° (initial value); + 56·3° (1 hr.); + 25·2° (2 hrs.); − 18·5° (3·5 hrs.); − 44·5° (5·5 hrs.); − 80·0° (8 hrs.); − 100° (11 hrs.); − 111·8° (13 hrs.); − 115·9° (16 hrs.); − 117·6° (18 hrs.). The solution was neutralised with barium carbonate and filtered, and the precipitate washed with hot water. The combined filtrates, which were only slightly reducing to Fehling's solution, were evaporated to a syrup (0·69 g.) the specific rotation of which was − 99·5° in water (*c*, 6·87). This was boiled with acetic anhydride (20 c.c.) and sodium acetate (2 g.) for 20 minutes, poured into water, neutralised with sodium bicarbonate, extracted with chloroform, and the extract dried ($MgSO_4$). Evaporation of the solvent gave a thick syrup which distilled at 130—150° (bath temp.)/0·01 mm. The distillate set on cooling to a hard glass which partly crystallised on treatment with alcohol. The crystals were collected and recrystallised from alcohol; large prisms, m. p. 90—91°, $[\alpha]_D^{17°}$ − 212 2° in chloroform (*c*, 0·452). Yield, 0·2 g. The compound was 2-*chloro* 3 : 4-*diacetyl* 1 : 6-*anhydro β-altrose* (Found: C, 45·9; H, 5·2; Cl, 12·3. $C_{10}H_{13}O_6Cl$ requires C, 45·5; H, 5·0; Cl, 13·5%).

Hydrolysis of 3-Chloro α-Methylglucoside [Fraction (II)].—(a) *With 5% sulphuric acid.* The substance (1·56 g.) was dissolved in sulphuric acid (30 c.c., 5%) (*c*, 5·218) and the solution heated at 100°: $[\alpha]_D$ + 145·3° (initial value); + 145·1° (½ hr.); + 143·5° (1½ hrs.); + 140·0° (5½ hrs.); + 134·6° (8 hrs.); + 128·2° (14½ hrs.); + 127·6° (17 hrs.). These figures show that hydrolysis was slow. The solution, which was reducing to Fehling's solution, was neutralised with barium carbonate, and the precipitate was filtered off and washed with hot water. On evaporation of the combined filtrates, a crystalline product was obtained. This was recrystallised from ethyl acetate; it had m. p. 136—138° (0·5 g.) and was unchanged starting material. It was accompanied by a non-crystalline product.

(b) *With 15% sulphuric acid.* The syrup and crystals from (a) (1·31 g.) were dissolved in sulphuric acid (25 c.c., 15%) (*c*, 5·25) and the solution heated at 100°: $[\alpha]_D$ + 119·3° (initial value); + 120·0° (½ hr.); + 121·2° (2½ hrs.); + 111·9° (9½ hrs.); + 100·2° (16½ hrs.); + 103·0° (20 hrs.). These figures show that the reaction was proceeding still very slowly and on working up the product as before a small amount of the original crystalline substance, m. p. 136°, was recovered (0·2 g.), together with the syrupy material.

(c) *With 25% sulphuric acid.* The crystalline substance, m. p. 136° (4·5 g.), was dissolved in sulphuric acid (75 c.c., 25%) (*c*, 6·0) and the solution boiled under reflux until a constant rotation value was reached: $[\alpha]_D$ + 135° (initial value); + 80·5° (½ hr.); + 66·5° (1 hr.); + 111·2° (2½ hrs.); + 32·2° (4 hrs.); + 30·2° (5·5 hrs.). The solution, reducing to Fehling's solution, was neutralised with barium carbonate, and the precipitate filtered off, and washed with hot water; the combined filtrates were evaporated. The residue was crystalline and on recrystallisation from alcohol gave colourless prisms, m. p. 155—156°;

$[\alpha]_D^{20°}$ + 64·1° in water (*c*, 2·215). It was *3-chloro glucose*. Yield, 2·5 g. (Found: C, 36·4; H, 5·5 $C_6H_{11}O_5Cl$ requires C, 36·4; H, 5·5%).

Hydrolysis of α-Methylglucoside with 10% Sulphuric Acid.—α-Methylglucoside (1 g.) was dissolved in sulphuric acid (25 c.c., 2N) (*c*, 4·0) and heated at 100° until the rotation was constant: $[\alpha]_D$ + 156° (initial value); + 133° (½ hr.); + 119° (1 hr.); + 96° (2 hrs.); + 77° (3 hrs.); + 65° (4 hrs.); + 61° (5 hrs.); + 58° (6 hrs.); + 57° (7 hrs.).

Condensation of 3-Chloro Glucose with Acetone.—3-Chloro glucose (0·5 g.) was shaken with acetone (40 c.c.) containing concentrated sulphuric acid (0·2 c.c.). Solution was complete within ½ hour. After 12 hours the acid was neutralised with anhydrous sodium carbonate and the inorganic material filtered off and washed with acetone. The combined filtrates were evaporated and the residue was extracted with chloroform. On evaporation of the solvent, a syrup (0·8 g.) was obtained. This distilled in the presence of barium carbonate as a colourless liquid (0·3 g.), b. p. 155° (bath temp.)/0·02 mm.; $n_D^{22°}$ 1·4612; $[\alpha]_D^{21°}$ − 18·2° in chloroform (*c*, 0·88). It was *3-chloro diacetone glucose* (Found: C, 52·0; H, 7·2. $C_{12}H_{19}O_5Cl$ requires C, 51·9; H, 6·8%).

Condensation of 2-Chloro α-Methylaltroside [Fraction (I)] with Benzaldehyde.—The substance (0·7 g.) was shaken with benzaldehyde (15 c.c.) and zinc chloride (0·5 g.) for 3 days, by which time solution was complete. Sodium carbonate (0·5 g.) dissolved in water was added and the solution steam distilled in a vacuum until all benzaldehyde had been removed. After evaporation to dryness, the residue was extracted with chloroform. On evaporation of the solvent, a residue was obtained which only crystallised to a small extent. The crystalline substance was 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside (20 mg.), m. p. 197—198°, doubtless formed during the process of isolation. The main syrup, however, could not be crystallised. The experiment was repeated with the same result.

Treatment of 3-Chloro 4 : 6-Benzylidene α-Methylglucoside with Sodium Methoxide.—The substance (40 mg.) was dissolved in chloroform (2 c.c.) and a solution of sodium (3 mg., 1 mol.) in methyl alcohol (2 c.c.) added with cooling. Next day the solution was diluted with an equal volume of water and exhaustively extracted with chloroform. The extract was evaporated after drying ($MgSO_4$), leaving a crystalline residue. This on recrystallisation from alcohol gave 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside (16 mg.), m. p. 199° undepressed in admixture with an authentic specimen.

3-Chloro 4 : 6-Benzylidene 2-Methyl α-Methylglucoside.—3-Chloro 4 : 6-benzylidene α-methylglucoside (1·1 g.) was treated thrice with methyl iodide and dry silver oxide at 45°. After each treatment, the methyl iodide was distilled off and the residue extracted with boiling chloroform. At the conclusion of the third treatment, the *product* was recrystallised from alcohol in needles, m. p. 145—146°; $[\alpha]_D^{20°}$ + 46·4° in acetone (*c*, 0·926). Yield, 0·9 g. (Found: C, 57·5; H, 6·0; Cl, 11·5; OMe, 19·4. $C_8H_{15}O_5Cl$ requires C, 57·3; H, 6·1; Cl, 10·3; OMe, 19·7%).

Attempted Hydrogenation of 3-Chloro 4 : 6-Benzylidene 2-Methyl α-Methylglucoside.—The compound (0·85 g.) suspended in dry methyl alcohol (100 c.c.) containing potassium hydroxide (0·2 g.) was heated with hydrogen in the presence of Raney nickel at 130°/100 atm. for 6 hours. No reaction took place, and the unchanged 3-chloro 4 : 6-benzylidene 2-methyl α-methylglucoside was recovered. The experiment was repeated at 180°/100 atm. for 6 hours but again no reaction took place. A final attempt was made at 220°/125 atm. for 6 hours, but this resulted in complete destruction of the compound.

Attempted Reaction of 3-Chloro 4 : 6-Benzylidene α-Methylglucoside with Sodium Iodide in Acetone.—The compound (0·43 g.) was dissolved in dry acetone (50 c.c.) containing dry sodium iodide (0·6 g.). The solution was heated in a sealed tube at 100° for 48 hours. No sodium chloride separated and, after the solvent had been removed and the product washed with water and recrystallised from alcohol, starting material was recovered, m. p. 163—165° (0·38 g.). No reaction had occurred.

Treatment of 3-Chloro 4 : 6-Benzylidene 2-Methyl α-Methylglucoside with Potassium Hydroxide.—(*a*) The compound (0·8 g.) was dissolved in acetone (45 c.c.) and water (200 c.c.) containing potassium hydroxide (1·2 g.). The mixture, which was not homogeneous, was boiled under reflux for 9 hours with frequent shaking. It was then diluted with water and extracted with chloroform. The extract, after being dried ($MgSO_4$), was evaporated; the residue on recrystallisation from alcohol had m. p. 143—145° alone or in admixture with the original compound. Yield, 0·7 g.

(*b*) The recovered compound (0·7 g.) was heated with alcoholic potash (1·2 g. KOH in 75 c.c. of alcohol) at 130° in a sealed tube for 48 hours. The product, which was very dark in colour, and had clearly suffered extensive decomposition, was diluted with water and extracted with chloroform. The extract after being dried ($MgSO_4$) and evaporated yielded only starting material, m. p. 141—143° alone or in admixture with the original pure compound. Yield, 0·48 g.

Treatment of 4 : 6-Benzylidene 2 : 3-Anhydro α-Methylalloside with Hydrobromic Acid.—The alloside (7 g.) was dissolved in acetone (500 c.c.) and hydrobromic acid (20 c.c., 2N) added. The solution was boiled under reflux for 4 hours. The acid was then neutralised with lead carbonate and the inorganic material filtered off and washed with acetone. The aqueous solution was extracted with ether to remove free benzaldehyde. On evaporation of the ether and subsequent steam distillation in a vacuum to remove benzaldehyde and evaporation to dryness, a syrup was obtained. This was dissolved in ether, the solution filtered, and the solvent removed. A low-melting crystalline substance was obtained which was recrystallised with some difficulty from ethyl acetate–light petroleum; it formed prisms, m. p. 65—67°; $[\alpha]_D^{15°}$ + 42·2° in chloroform (*c*, 0·945). This compound has so far not been identified.

The aqueous solution, after ether extraction, was evaporated to dryness under diminished pressure and the residue extracted with boiling ethyl acetate. This extract on being evaporated gave a crystalline residue which was fractionally recrystallised from alcohol. Fraction (A) (0·65 g.) crystallised in prisms, m. p. 153—153·5°; $[\alpha]_D^{17°}$ + 86·2° in alcohol (*c*, 0·487) (Found: C, 32·6; H, 5·1; Br, 29·8. $C_7H_{13}O_5Br$ requires C, 32·7; H, 5·0; Br, 31·1%). Evaporation of the mother liquors and recrystallisation of the residue from ethyl acetate gave fraction (B) (1·9 g.) in needles, m. p. 132—133°; $[\alpha]_D^{15°}$ + 109·8° in alcohol (*c*, 0·437) (Found: C, 32·2; H, 5·2; Br, 31·5%). Fractions (A) and (B) are subsequently shown to be *2-bromo α-methylaltroside* and *3-bromo α-methylglucoside* respectively.

On evaporation of the mother liquors a syrupy residue (1·0 g.) was obtained which could not be

crystallised. This was shaken with benzaldehyde (10 c.c.) and zinc chloride (0·5 g.) for 24 hours. Sodium carbonate (0·5 g.) was added and the benzaldehyde removed by steam distillation under reduced pressure. The dry residue was extracted with chloroform; on evaporation of the extract, a crystalline residue was obtained which recrystallised from alcohol in feathery needles, m. p. 174—175°. Yield, 1·1 g. $[\alpha]_D^{16°}$ + 12·8° in chloroform (*c*, 2·336) (Found: C, 49·0; H, 4·8; Br, 24·1. $C_{14}H_{17}O_5Br$ requires C, 48·7; H, 4·9; Br, 23·2%).

Condensation of Fraction (B) with Benzaldehyde.—The crystalline substance, m. p. 132° (6·3 g.), was shaken for 24 hours with benzaldehyde (100 c.c.) and zinc chloride (6·3 g.). Sodium carbonate (8·5 g.) was added, and the benzaldehyde removed by steam distillation under reduced pressure. The dry residue was extracted with chloroform and the extract evaporated. A crystalline residue was obtained which was recrystallised from alcohol giving feathery needles, m. p. 175° undepressed in admixture with the benzylidene compound obtained above; it was *3-bromo* 4 : 6-*benzylidene α-methylglucoside.*

The yield of fraction (A) was 9·6%, and that of fraction (B) (including the part isolated as the benzylidene derivative) was 41%.

Condensation of Fraction (A) with Acetone.—The substance (0·9 g.) was shaken with acetone (40 c.c.) containing concentrated sulphuric acid (0·2 c.c.). Solution took place almost immediately, and after 24 hours the acid was neutralised with anhydrous sodium carbonate. The inorganic material was filtered off and washed with acetone and the combined filtrates were evaporated to a thick syrup. This was distilled in the presence of barium carbonate; b. p. 140° (bath temp.)/0·01 mm. (Found: OMe, 10·4. $C_{10}H_{17}O_6Br$ requires OMe, 10·4%). The distillate subsequently crystallised and was recrystallised from ether–light petroleum in prisms, m. p. 64—66°; $[\alpha]_D^{15°}$ + 43·1° in chloroform (*c*, 1·068) (Found: C, 39·9; H, 5·8. $C_{10}H_{17}O_6Br$ requires C, 40·4; H, 5·7%); it was *2-bromo* 3 : 4-*monoacetone α-methyl-altroside.*

Attempted Condensation of Fraction (B) with Acetone.—The substance (0·3 g.) was shaken with acetone (40 c.c.) containing concentrated sulphuric acid (0·2 c.c.). Solution was complete in 2 hours; after 24 hours the acid was neutralised with anhydrous sodium carbonate and the inorganic material filtered off and washed with acetone. The combined filtrates were evaporated in the presence of sodium carbonate and the residue was extracted with hot ethyl acetate. Evaporation of the solvent gave a syrup which crystallised on trituration with alcohol. It was recrystallised from alcohol; m. p. 130—132° (0·3 g.) undepressed in admixture with the starting material.

Hydrolysis of Fraction (A) with 5% Sulphuric Acid.—The substance (0·29 g.) was dissolved in sulphuric acid (15 c.c. 5%) (*c*, 1·94) and heated at 100° until the rotation was constant. $[\alpha]_D$ + 73·1° (initial value); + 45·4° (5 mins.); + 17·5° (15 mins.); − 28·9° (1 hr.); − 45·4° (1½ hrs.); − 49·5° (2 hrs.); − 55° (3 hrs.); − 55° (4 hrs.).

The sulphuric acid was neutralised with barium carbonate, and the precipitate filtered off and washed with hot water. The filtrate, which was only slightly reducing to Fehling's solution, was evaporated under reduced pressure and the residue extracted with boiling alcohol. Evaporation of the alcohol gave a glassy residue (0·3 g.) which contained barium salts. It was then boiled under reflux with acetic anhydride (10 c.c.) and sodium acetate (0·5 g.) for 10 mins. After being poured into water, the solution was neutralised with sodium bicarbonate and extracted with chloroform. Evaporation of the solvent gave a thick syrup (0·2 g.) which distilled at 160—190° (bath temp.)/0·01 mm. The distillate (0·07 g.) had $[\alpha]_D^{20°}$ − 68·0° in chloroform (*c*, 1·055), and probably contained 2-bromo 3 : 4-diacetyl 1 : 6-anhydro β-altrose (Found: Br, 17·7, 17·1. Calc. for $C_{10}H_{13}O_6Br$: Br, 24·9%).

Hydrolysis of Fraction (B) with Sulphuric Acid.—The substance (1·66 g.) was dissolved in sulphuric acid (25 c.c., 10%) (*c*, 6·652) and the solution boiled under reflux until constant rotation was reached. $[\alpha]_D$ + 116·5° (initial value); + 91° (15 mins.); + 80·5° (30 mins.); + 64·0° (1 hr.); + 46·3° (2 hrs.); + 44·5° (3 hrs.); + 42·5° (4½ hrs.). The solution, which was reducing to Fehling's solution, was neutralised with barium carbonate, and the precipitate filtered off and washed with hot water. On evaporation of the combined filtrates a syrup was obtained (1·55 g.) which crystallised on trituration with alcohol. Recrystallisation from alcohol gave colourless prisms, m. p. 151°; $[\alpha]_D^{20°}$ + 60·9° in water (*c*, 2·530). It was *3-bromo glucose* (Found: C, 30·0; H, 4·97. $C_6H_{11}O_5Br$ requires C, 29·6; H, 4·54%).

Condensation of Fraction (A) with Benzaldehyde.—The substance (0·5 g.) was shaken for 12 hours with benzaldehyde (10 c.c.) and zinc chloride (0·5 g.). Anhydrous sodium carbonate (0·5 g.) was then added, the excess of benzaldehyde removed by steam distillation under reduced pressure, and the dry residue extracted with hot chloroform. Evaporation of the chloroform gave a semi-crystalline residue (0·3 g.) from which was crystallised 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside, m. p. 198—199° alone or in admixture with an authentic specimen.

Treatment of 3-Bromo 4 : 6-Benzylidene α-Methylglucoside with Sodium[4] Methoxide.—The substance (0·1 g.) was dissolved in chloroform (4 c.c.) and a solution of sodium (8 mg., 1 mol.) in methyl alcohol (4 c.c.) added with cooling. After 12 hours the solution was diluted with water and extracted with chloroform. Evaporation of the solvent after drying ($MgSO_4$) gave a crystalline residue which was recrystallised from alcohol in feathery needles, m. p. 198—199° undepressed in admixture with 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside. Yield, 0·04 g.

3-Bromo 4 : 6-Benzylidene 2-Methyl α-Methylglucoside.—3-Bromo 4 : 6-benzylidene α-methylglucoside (7·1 g.) was heated thrice with methyl iodide and dry silver oxide at 45°. After each treatment the methyl iodide was distilled off and the residue extracted with boiling chloroform. After the third treatment, the product was recrystallised from alcohol in feathery needles, m. p. 168—168·5°; $[\alpha]_D^{18°}$ + 7·8° in alcohol (*c*, 0·511). Yield, 6·6 g. (Found: C, 50·3; H, 5·3; Br, 21·3. $C_{15}H_{19}O_5Br$ requires C, 50·1; H, 5·3; Br, 22·3%).

4 : 6-Benzylidene 2-Methyl 3-Deoxy-α-methylglucoside.—3-Bromo 4 : 6-benzylidene 2-methyl α-methylglucoside (0·5 g.) was suspended in methyl alcohol (50 c.c.) containing potassium hydroxide (0·25 g.) and shaken with hydrogen over Raney nickel at room temperature. 120 C.c. (N.T.P.) of hydrogen were rapidly absorbed. The catalyst was filtered off and the alcohol evaporated. The residue was washed with water, and recrystallised from alcohol in feathery needles, m. p. 79—80°; $[\alpha]_D^{20°}$ + 81·6°

in alcohol (*c*, 4·54). Yield, 0·3 g. (Found: C, 63·7; H, 7·0. Calc. for $C_{15}H_{20}O_5$: C, 64·3; H, 7·1%). Prins (*loc. cit.*) gives m. p. 79—80°; $[\alpha]_D$ + 83° in chloroform.

Treatment of 4 : 6-*Benzylidene* 2 : 3-*Anhydro* α-*Methylalloside with Sulphuric Acid.*—The alloside (10 g.) was dissolved in acetone (1 l.), sulphuric acid (29 c.c., 2N) added, and the solution boiled under reflux for 4 hours. The acid was then neutralised with barium carbonate and the inorganic precipitate filtered off and washed with acetone. The combined filtrates were evaporated until free from acetone and the aqueous solution was extracted with ether. On evaporation of the ether and subsequent distillation of the benzaldehyde in steam, a syrup (0·5 g.) remained on evaporation to dryness. This rapidly crystallised on addition of alcohol and on recrystallisation from alcohol was obtained in needles, m. p. 146—147°; $[\alpha]_D^{15°}$ + 11·6° in chloroform (*c*, 1·035). This compound has not been identified.

The aqueous solution, after ether extraction, was evaporated to dryness under diminished pressure. The residual syrup (5·5 g.) partially crystallised on addition of alcohol; recrystallisation from alcohol gave α-methylglucoside, m. p. 165° undepressed in admixture with an authentic specimen. Yield, 0·5 g. Evaporation of the mother liquors gave a syrup (4·8 g.), which could not be crystallised. It was shaken with benzaldehyde (50 c.c.) and zinc chloride (4 g.) for 24 hours. The solution was poured into water–light petroleum and the precipitate recrystallised from alcohol; m. p. 197—199° undepressed in admixture with 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside. Yield, 4 g. Evaporation of the mother liquors provided a further 1·4 g. of syrup which could not be crystallised. It was not possible to isolate any of the altrose isomer which may have been formed.

Hydrolysis of 4 : 6-*Benzylidene* 2 : 3-*Anhydro* α-*Methylalloside with Oxalic Acid.*—The procedure adopted was that of Robertson and Dunlop (*loc. cit.*), namely, hydrolysis of the alloside (10 g.) in acetone solution (450 c.c.) containing oxalic acid (15 g. in 50 c.c. of water) by heating under reflux for 24 hours. The acid was removed as insoluble barium oxalate, and the acetone evaporated. Free benzaldehyde was removed by extraction with ether. On evaporation of the aqueous layer, a partly crystalline syrup was obtained; on recrystallisation from alcohol, α-methylglucoside separated, m. p. 164—165°. Yield, 0·8 g. A syrup (2·8 g.) was obtained on evaporation of the mother liquors, but this, which was presumably 2 : 3-anhydro α-methylalloside, could not be crystallised.

THE A.E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM.

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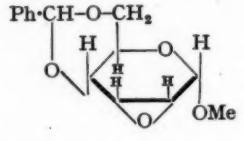
4. *Some Observations on the Ring Scission of* 4 : 6-*Benzylidene* 2 : 3-*Anhydro* α-*Methylmannoside with Ammonia.*

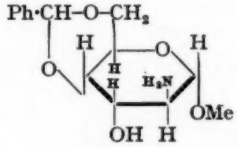
By L. F. WIGGINS.

The secondary product of the anhydro ring scission of 4 : 6-benzylidene 2 : 3-anhydro α-methylmannoside with ammonia is shown not to be a derivative of glucosamine but a secondary amine. The product of Myers and Robertson (*J. Amer. Chem. Soc.*, 1943, **65**, 8), obtained by the hydrolysis of 3-amino 4 : 6-benzylidene α-methylaltroside, is not Fischer's methyl "epiglucosamine" but 3-amino 1 : 6-anhydro altrose.

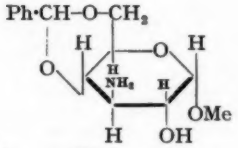
IT has been generally held hitherto that the ring scission, with ammonia, of an ethylene oxide anhydro ring compound of the sugar series, in which the ring does not involve a primary carbon atom, takes place with Walden inversion and gives rise to two isomeric amino sugar derivatives, which it may or may not be possible to isolate depending on their ease of separation. Thus, 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside (I) gave 2-amino 4 : 6-benzylidene α-methylaltroside (II) together with 3-amino 4 : 6-benzylidene α-methylglucoside (III) (Peat and Wiggins, *J.*, 1938, 1810). Similarly James, Smith, Stacey, and Wiggins (*Nature*, 1945, **156**, 308) have shown that the ethylene oxide ring in 1 : 6-2 : 3-dianhydro β-talose (IV) opens under the influence of ammonia giving 2-amino 1 : 6-anhydro β-galactose (V) and 3-amino 1 : 6-anhydro β-idose (VI).



(I.)



(II.)



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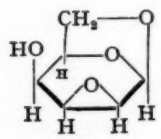

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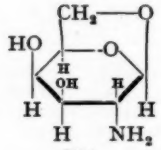

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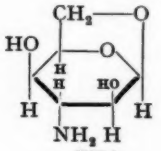
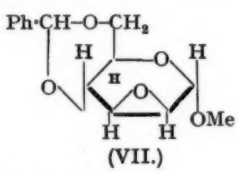
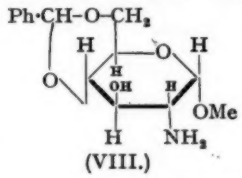
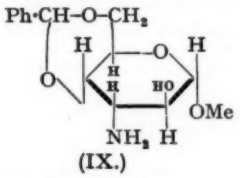


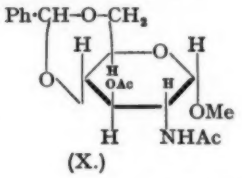
(VI.)

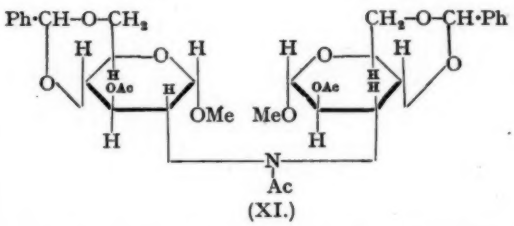
An instance in which this general scheme does not hold has now been found. Myers and Robertson (*loc. cit.*) treated 4 : 6-benzylidene 2 : 3-anhydro α-methylmannoside (VII) with ammonia. According to the general theory outlined above they should have obtained two compounds, 2-amino 4 : 6-benzylidene α-methylglucoside (VIII) (a glucosamine derivative) and 3-amino 4 : 6-benzylidene α-methylaltroside (IX), and indeed these authors did obtain two compounds which they believed were the derivatives of glucose and altrose [(VIII) and (IX)]. This assumption was natural, since ring scission of a very similar compound, 4 : 6-dimethyl 2 : 3-anhydro β-methylmannoside, had already been carried out with the formation of 2-acetamido 4 : 6-dimethyl β-methylglucoside (a glucosamine derivative) and 3-acetamido 4 : 6-dimethyl β-methylaltroside (Haworth, Lake, and Peat, *J.*, 1939, 274), Myers and Robertson had isolated 3-amino 4 : 6-benzylidene α-methylaltroside (IX) (A) as the main product, and the secondary product (B), supposedly a glucosamine derivative (2-acetamido 3-acetyl 4 : 6-benzylidene α-methylglucoside), characterised as its acetate (X) in small yield. The present author has now carried out similar experiments and has obtained from (VII) the altroside (IX) (giving a diacetate, m. p. 196°) in 92·3% yield and the secondary component (isolated as a diacetate, m. p. 237°, $[\alpha]_D$ + 45·31°), the so-called glucosamine derivative, in small yield. The analytical figures, however, were not in agreement with the formulation of this secondary product as (X). Moreover, 2-*acetamido* 3-*acetyl* 4 : 6-*benzylidene* α-*methylglucoside* (X) was synthesised from natural glucosamine and this compound had constants (m. p. 203—205°, $[\alpha]_D$ + 33°) different from those of the product (B). It was clear either that the product (B) had resulted from a side reaction or that the general theory of anhydro ring scission was not applicable in this case.

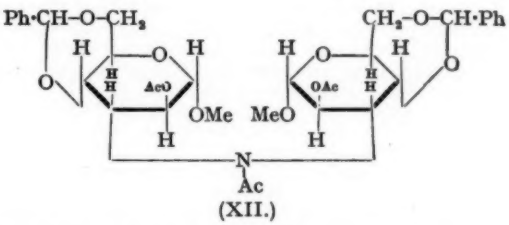

(VII.)


(VIII.)


(IX.)


(X.)


(XI.)


(XII.)

The *compound* (B) had a high melting point, and the analytical figures suggested that it contained one atom of nitrogen combined with two aldose residues. This idea was supported by the fact that a molecular weight determination (Rast) gave a value of 630 whereas (X) requires 365. The analysis of (B) conforms to one or other of the structures represented by (XI) and (XII), either of which could arise by the scission of the ethylene oxide ring of 4 : 6-benzylidene 2 : 3-anhydro α-methylmannoside (VII) through the agency of the basic 3-amino 4 : 6-benzylidene α-methylaltroside (IX) and subsequent acetylation of the product.

This reaction, of course, would be subsidiary to the main ring opening of the anhydro mannoside with ammonia whereby the 3-amino altroside is produced. This view was confirmed by the following synthesis. 4 : 6-Benzylidene 2 : 3-anhydro α-methylmannoside was treated with pure 3-amino 4 : 6-benzylidene α-methylaltroside; after acetylation of the product, a substance, tentatively represented by (XII), identical with the product (B) was obtained in quite good yield, although no other crystalline product could be isolated. It must be emphasised, however, that the representation of (B) by (XII) and not by (XI) is based solely on analogy with the observed effects of anhydro ring fission with simple reagents. Further work on the substance (B), with a view to a more definite elucidation of its structure, is being carried out.

The glucosamine derivative, 2-acetamido 3-acetyl 4 : 6-benzylidene α-methylglucoside, was synthesised as follows. *N*-Carbobenzoxy-α-methylglucosaminide (Neuberger, *J.*, 1939, 122) was converted by hydrogenation into α-methylglucosaminide and thence into the *N*-acetyl derivative which on treatment with benzaldehyde gave 2-acetamido 4 : 6-benzylidene α-methylglucoside from which 2-acetamido 3-acetyl 4 : 6-benzylidene α-methylglucoside was obtained by further acetylation.

Myers and Robertson (*loc. cit.*) claimed to have partially hydrolysed 3-amino 4 : 6-benzylidene α-methylaltroside (IX) with dilute aqueous hydrochloric acid and obtained what they described as 3-amino β-methylaltroside hydrochloride having m. p. 209° and $[\alpha]_D$ — 149° (in water) and as being identical with Fischer's methyl epiglucosamine hydrochloride (*Ber.*, 1920, **53**, 836). If this compound is in truth formed its formation must involve inversion on C_1 without loss of methoxyl, since the starting material is a derivative of α-methylaltroside. This is a rather unusual phenomenon since the reaction was carried out in aqueous medium. Moreover, it was observed by Peat and Cutler (*J.*, 1938, 274) that many derivatives of β-methylglucosaminide were converted almost quantitatively and irreversibly into the corresponding α-form. The present author, however, found that partial hydrolysis of (IX) with oxalic acid in acetone was possible and *3-amino α-methylaltroside*, m. p. 120°, $[\alpha]_D$ + 109·0°, and its *hydrochloride*, m. p. 208—209° (decomp.), $[\alpha]_D$ + 88·2°, were isolated. These compounds by virtue of their high positive rotations could certainly be fairly described as glucosides of the α-type. In order to try to clear up the anomaly presented by the work of Myers and Robertson, their experiments on the hydrolysis of 3-amino 4 : 6-benzylidene α-methylaltroside were repeated; the product isolated was *3-amino anhydro altrose hydrochloride* having m. p. 215—216° (decomp.) and $[\alpha]_D$ — 171·9°, and not Fischer's methyl epiglucosamine hydrochloride. This amino anhydro altrose was clearly identical with Levene and Meyer's (*J. Biol. Chem.*, 1923, **55**, 221) anhydro epiglucosamine, m. p. 216° (decomp.) and $[\alpha]_D$ — 172° (2·5% HCl), and although Levene and Meyer ascribed to it a 1 : 2-anhydro structure, in the light of modern work which has shown that altrose itself readily forms a 1 : 6-anhydride (altrosan) (Richtmyer and Hudson, *J. Amer. Chem. Soc.*, 1935, **57**, 1716; 1940, **63**, 961) it is fairly certain that the anhydro epiglucosamine is 3-amino 1 : 6-anhydro altrose.

Experimental

4 : 6-Benzylidene 2 : 3-anhydro α-methylmannoside was obtained according to the procedure of Robertson and Griffith (*J.*, 1935, 1193).

The Action of Ammonia on 4 : 6-*Benzylidene* 2 : 3-*Anhydro* α-*Methylmannoside.*—The anhydro mannoside (4 g.) was heated in a sealed tube with 200 c.c. of methyl alcohol (saturated with ammonia at 0°) at 130° for 48 hours. Evaporation of the solvent gave a solid residue (4·25 g.) which after careful fractional crystallisation gave (A) m. p. 190—191° (yield, 3·97 g.), and a syrupy residue (0·22 g.). The compound (A) was 3-amino 4 : 6-benzylidene α-methylaltroside and was obtained in 92·3% yield, assuming complete conversion of the anhydro sugar into amino sugars. It showed $[\alpha]_D$ + 93·8° in chloroform (*c*, 1·44) (Found : C, 59·4; H, 6·7; N, 5·4. Calc. for $C_{14}H_{19}O_5N$: C, 59·8; H, 6·8; N, 5·0%).

The syrupy residue showed $[\alpha]_D$ +90·6° in chloroform (*c*, 3·2). It was acetylated by dissolving it in pyridine (5 c.c.) and adding acetic anhydride (0·5 c.c.) and leaving at room temperature for 7 days. After being poured into water, the product was extracted with chloroform and the extract washed with dilute sulphuric acid, sodium bicarbonate solution, and with water, dried ($MgSO_4$), and evaporated. Yield, 0·16 g. of a syrup which partly crystallised. The crystalline *substance* (B) was isolated in thick needles by recrystallisation from alcohol. Yield, 0·025 g., m. p. 235—238°. Repeated recrystallisation raised the m. p. to 237—238°; $[\alpha]_D$ +45·3° in chloroform (*c*, 1·305) [Found : C, 60·9; H, 5·8; N, 1·9; *M*, 630 (Rast). $C_{34}H_{41}O_{13}N$ requires C, 60·8; H, 6·1; N, 2·1%; *M*, 671 (cf. Calc. for $C_{18}H_{23}O_7N$: C, 59·1; H, 5·8; N, 3·8%; *M*, 365)].

3-*Acetamido* 2-*Acetyl* 4 : 6-*Benzylidene* α-*Methylaltroside.*—3-Amino 4 : 6-benzylidene α-methylaltroside (0·4 g.) was dissolved in dry pyridine (5 c.c.), acetic anhydride (0·6 c.c.) added and the mixture kept overnight at room temperature. The mixture was poured into water and the *product* extracted with chloroform. The extract was washed with 5% sulphuric acid, sodium bicarbonate solution, and water, dried ($MgSO_4$), and the chloroform removed. The residual syrup crystallised on trituration with alcohol and recrystallised from alcohol in small prisms. Yield, 0·3 g.; m. p. 194—196°; $[\alpha]_D$ +20·0° in chloroform (*c*, 1·6) (Found : C, 59·6; H, 6·2; N, 4·0. $C_{18}H_{23}O_7N$ requires C, 59·1; H, 6·3; N, 3·8%).

Treatment of 4 : 6-*Benzylidene* 2 : 3-*Anhydro* α-*Methylmannoside with* 3-*Amino* 4 : 6-*Benzylidene* α-*Methylaltroside.*—The anhydro mannoside (0·3 g.) together with 3-amino 4 : 6-benzylidene α-methylaltroside (0·3 g.) was heated in dry methyl alcohol (100 c.c.) solution in a sealed tube at 150° for 12 hours. The solution was evaporated to a syrup which would not crystallise. It was acetylated by leaving it at room temperature for 24 hours with dry pyridine (15 c.c.) and acetic anhydride (8 c.c.). The product was isolated by pouring the mixture into water, when a crystalline precipitate was obtained. This was collected and, recrystallised from alcohol, formed stout needles. Yield, 0·16 g.; m. p. 237—238° not depressed in admixture with product (B) above; $[\alpha]_D$ +46·0° in chloroform (*c*, 1·395).

The mother liquors, after removal of the crystalline precipitate, were extracted with chloroform, and the extract was washed with dilute sulphuric acid, dilute sodium bicarbonate solution, and water, dried ($MgSO_4$), filtered, and evaporated. The residual syrup would not crystallise.

Partial Hydrolysis of 3-*Amino* 4 : 6-*Benzylidene* α-*Methylaltroside.*—The compound (2·3 g.) was dissolved in acetone (100 c.c.), oxalic acid (3·5 g.) dissolved in 20 c.c. of water added, and the mixture boiled for 15 hours and then evaporated to small bulk. Water (30 c.c.) was added and benzaldehyde removed by extraction with ether. Crystalline barium hydroxide (11·5 g.) was dissolved in water and added to the aqueous solution, the precipitated barium oxalate removed by filtration, and excess of Ba^{++} removed by titration with N-sulphuric acid, so that neither Ba^{++} nor SO_4^{--} was present. The

filtered solution was evaporated to dryness, and the crystalline residue was recrystallised, with some difficulty, from dioxan. Yield, 0·6 g.; m. p. 120°. A syrupy residue (C) remained. The crystalline *substance* showed $[\alpha]_D$ +109·9° in water (*c*, 2·985) (Found: C, 43·8; H, 7·8; N, 7·9. $C_7H_{15}O_5N$ requires C, 43·5; H, 7·9; N, 7·3%). It gave a crystalline *hydrochloride* on titration with hydrochloric acid, followed by evaporation and recrystallisation from alcohol–water, m. p. 208° (decomp.); $[\alpha]_D^{17°}$ +88·2° in water (*c*, 1·15) (Found: Cl, 15·4. $C_7H_{15}O_5N,HCl$ requires Cl, 15·5%).

The syrupy residue (C) showed $[\alpha]_D^{17°}$ +73° in water (*c*, 2·745) and this also yielded the same hydrochloride after titration with hydrochloric acid. Yield, 0·7 g.

This substance was heated under reflux with 1% methyl alcoholic hydrogen chloride for 18 hours but there was only a small decrease in the specific rotation and clearly no complete change over to the β-form had occurred; + 93·7° (initial); + 84·4° (¼ hr.); + 78·1° (2¾ hrs.); + 78·1° (5 hrs.); + 74·0° (9 hrs.); + 75° (18 hrs.). The initial hydrochloride was recovered in 50% yield after this treatment.

Treatment of 3-*Amino* 4 : 6-*Benzylidene* α-*Methylaltroside with* 1% *Hydrochloric Acid.*—The substance (1 g.) was dissolved in 160 c.c. of 1% aqueous hydrochloric acid and the solution heated at 100° for 28 hours (Myers and Robertson, *loc. cit.*). The $[\alpha]_D$ changed as follows: + 90·0° (initial value); + 72·0° (1½ hrs.); + 68·6° (4 hrs.); + 60·0° (10 hrs.); + 22° (15 hrs.); + 11° (20 hrs.); + 9° (24 hrs.); + 8° (28 hrs.). At this stage the solution was evaporated under diminished pressure. The *product*, twice recrystallised from alcohol–acetone–water in small prisms, was isolated in small yield, and had m. p. 215—216° (decomp.) (turned grey at 200°); $[\alpha]_D$ − 171·9° in water, − 172·2° in 2·5% hydrochloric acid (Found: C, 36·2; H, 6·1; N, 7·3. $C_8H_{11}O_4N,HCl$ requires C, 36·1; H, 6·1; N, 7·1%). It was 3-amino-1 : 6-anhydro altrose hydrochloride. Myers and Robertson (*loc. cit.*) give m. p. 209° (decomp.), $[\alpha]_D$ − 149° in water for their product alleged to be 3-amino β-methylaltroside. Levene and Meyer (*loc. cit.*) give m. p. 216° (decomp., changing colour at 190°), [α] − 172° in 2·5% hydrochloric acid for their anhydro epiglucosamine hydrochloride.

Synthesis of 2-*Acetamido* 3-*Acetyl* 4 : 6-*Benzylidene* α-*Methylglucoside.*—*N*-Carbobenzoxyglucosamine prepared by the method of Chargraff and Bovarnick (*J. Biol. Chem.*, 1937, **118**, 421) was converted into the corresponding α-methylglucosaminide according to Neuberger (*loc. cit.*) and subsequently hydrogenated over Raney nickel at 150° for 7 hours at 80°. The filtered solution was evaporated to a syrup and acetylated with methyl alcoholic acetic anhydride. The resulting crystalline *N*-acetyl α-methylglucosaminide was benzylidenated without further purification and *N*-acetyl 4 : 6-benzylidene α-methylglucosaminide isolated, m. p. 255—256°; $[\alpha]_D$ + 40·0° in chloroform (*c*, 1·5). Neuberger (*J.*, 1941, 507) gave m. p. 255°; $[\alpha]_D$ + 19°. The 2-acetamido 4 : 6-benzylidene α-methylglucosaminide (0·5 g.) was dissolved in pyridine (10 c.c.), acetic anhydride (2 c.c.) added, and the mixture left at room temperature for 48 hours. Thereafter it was poured into water and the *product* extracted with chloroform. The extract was washed with dilute sulphuric acid, sodium bicarbonate solution, and water. After being dried ($MgSO_4$), the chloroform extract was evaporated and the crystalline residue recrystallised from methyl alcohol; m. p. 203—205°; $[\alpha]_D$ + 33·0°. Yield, 0·3 g. (Found: C, 59·2; H, 6·1. $C_{18}H_{23}O_7N$ requires C, 59·2; H, 6·3%). The corresponding compound of the β-series is described by Myers and Robertson (*J. Amer. Chem. Soc.*, 1943, **65**, 8) and has m. p. 158° and $[\alpha]_D$ − 12·9° in chloroform.

The author desires to express his thanks to Professor W. N. Haworth, F.R.S., for the interest he has shown in this work.

THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM 15. [*Received, April 17th*, 1946.]

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5. *The Constitution of Yeast Ribonucleic Acid. Part X. Further Studies on the Nature of the Carbohydrate Radicals.*

By GEOFFREY R. BARKER, (MRS.) KATHLEEN R. FARRAR, and J. MASSON GULLAND.

The carbohydrate radicals of the purine nucleotides of yeast pentose nucleic acid are shown to be *d*(−)-ribose by identification of the corresponding aldonic acids as benziminazoles. Results previously reported (*J.*, 1943, 625; 1944, 339), suggesting that some *d*-arabinose might also be present, are now proved to have been due to epimerisation during the condensation of *d*-ribonic acid with *o*-phenylenediamine; the course of the reaction is dependent on the concentration of hydrogen chloride, and leads to ribobenziminazole alone when this is sufficiently high.

AN examination of the literature having revealed inconsistencies in the designations of the carbohydrate radicals of the pentose nucleic acids, attempts were made (Barker and Gulland, *J.*, 1943, 625) to establish the nature of the sugar of the pentose nucleic acid of yeast by formation of benziminazoles (Moore and Link, *J. Biol. Chem.*, 1940, **133**, 293) from the corresponding aldonic acids. Since the same benziminazole was obtained from synthetic barium *d*-ribonate (Steiger, *Helv. Chim. Acta*, 1936, **19**, 189) and from the aldonic acids produced by oxidation of the carbohydrate radicals liberated during acid hydrolysis of yeast pentose nucleic acid and the guanylic, adenylic, and cytidylic acids derived from it, it was concluded that these sugar radicals were *d*(−)-ribose.

After that investigation had been completed, however, the properties of *d*-ribobenziminazole

were reported both by Dimler and Link (*J. Biol. Chem.*, **1943**, **150**, 345), and by Richtmyer and Hudson (*J. Amer. Chem. Soc.*, **1942**, **64**, 1612) as being completely different from those found by us. The behaviour of *d*-ribonic acid was therefore re-examined, and *d*-ribobenziminazole was obtained (Barker, Cooke, and Gulland, *J.*, **1944**, 339), having properties corresponding with those observed by the American authors. The properties of the compound previously obtained by us were the same as those of *d*-arabobenziminazole, and the identity was confirmed by direct comparison with a sample prepared from synthetic *d*-arabonic acid obtained by oxidation of *d*(−)-arabinose; the melting point of our *d*-arabobenziminazole is, however, rather higher than that given by Moore and Link (*loc. cit.*). It seemed, therefore, that yeast pentose nucleic acid might contain *d*(−)-arabinose. The present investigations, limited to the sugar radicals associated with the purine bases in the nucleic acid, were designed to test this point.

By using the method of isolating *d*-ribobenziminazole recommended by Dimler and Link (*loc. cit.*, and private communication), it was found that our failure to isolate this compound in previous experiments was due to its high solubility, particularly in the presence of inorganic salts. Nevertheless, the aldonic acid obtained from guanosine still yielded *d*-arabobenziminazole as before in some experiments, in addition to *d*-ribobenziminazole. Furthermore, since this result was obtained using apparently identical samples of guanosine prepared from yeast nucleic acid supplied by both British Drug Houses and The Pharmaco-Chemical Products Co., it seemed likely that the formation of two products was to be ascribed not to the composition of any particular specimen of nucleic acid but rather to the mechanisms of the breakdown of the molecule or of the production of the benziminazole. Subsequent experiments confirmed this view since either *d*-ribobenziminazole or a mixture of this and *d*-arabobenziminazole could be produced at will. They also confirmed that these two commercial specimens of yeast nucleic acid were identical as regards the carbohydrate radicals of their purine nucleotides.

Dimler and Link (*loc. cit.*) point out that if oxidation of *d*(−)-ribose is carried out with alkaline hypoiodite, epimerisation results in the formation of some *d*-arabobenziminazole. This could, no doubt, explain the isolation by us of *d*-arabobenziminazole from yeast nucleic acid as previously reported, since oxidation was then carried out with alkaline hypoiodite, but in the experiments with nucleotides hydrolysis and oxidation were achieved simultaneously with hydrogen bromide and bromine. In the present investigations in which *d*-ribobenziminazole alone was formed, sugars were oxidised by bromine in the presence of barium benzoate (Hudson and Isbell, *J. Res. Nat. Bur. Stand.*, **1929**, **3**, 57), and parallel experiments using simultaneous hydrolysis and oxidation gave identical results. It was therefore concluded that *d*-arabonic acid was not formed during oxidation in acid solution. The possibility that *d*-ribobenziminazole suffered epimerisation in the feebly alkaline solution used in its preparation (see Experimental section) was excluded by the failure of deliberate attempts to effect this change.

It was also found that the nature of the benziminazoles produced was not dependent on the method used for disrupting the molecule of nucleic acid, since the same results were obtained whether it was broken down initially into nucleotides by cold alkali, or into nucleosides by hot aqueous pyridine, or by refluxing with acid whereby the sugar is liberated directly.

It was observed, however, that, quite independently of the technique used for hydrolysis and oxidation, either ribobenziminazole alone or ribobenziminazole together with arabobenziminazole could be produced by varying the quantity of hydrogen chloride used in the condensation of the aldonic acid with *o*-phenylenediamine. Thus one and the same sample of calcium aldonate obtained from guanosine, when condensed in presence of 2·48 molecular equivalents of hydrogen chloride yielded only *d*-ribobenziminazole, whereas in the presence of 1·4 molecular equivalents both ribobenziminazole and arabobenziminazole were isolated. In a parallel experiment with a different sample of calcium aldonate both benziminazoles were obtained using 1·98 molecular equivalents. It is therefore concluded that variations in the conditions of condensation alone account for the anomalous results and that, providing they are satisfactorily controlled, only *d*-ribobenziminazole is obtained from *d*-ribonic acid. The decision that the use of the higher, and not the lower, concentration of hydrogen chloride gave the correct result is justified by the formation of *d*-ribonic phenylhydrazide alone, but not *d*-arabonic phenylhydrazide, from ribonic acid which yielded ribobenziminazole either alone or mixed with arabobenziminazole according to the conditions of condensation with *o*-phenylenediamine (*J.*, **1943**, 625; **1944**, 339). Levene's conclusion that *d*(−)-ribose is the carbohydrate constituent of the purine nucleotides of yeast pentose nucleic acid is thus confirmed.

Care is required in the application of the benziminazole technique to the identification of sugars. Thus, consideration of the conditions recommended by Dimler and Link (*loc. cit.*) for preparing *d*-ribobenziminazole indicates that the formation of arabobenziminazole, which did

not occur, should not have been expected. On the other hand, repeated attempts have so far failed to yield *l*-ribobenziminazole in the condensation of calcium arabonate [prepared from *l*(+)-arabinose] with *o*-phenylenediamine in presence of hydrogen chloride in an amount insufficient to prevent epimerisation of calcium ribonate. Moore and Link (*J. Org. Chem.*, 1940, **5**, 637) state that in absence of hydrogen chloride epimerisation occurs at 135—150°; they isolated lyxobenziminazole from the condensation of *o*-phenylenediamine and xylonic acid, and add that this epimerisation is prevented by acid catalysts. In some of the condensations described in our two previous papers, phosphoric acid, as well as hydrogen chloride, was used to aid interaction, but had no effect on the course of the reaction which seemed to be guided by the concentration of hydrogen chloride. Determination of the chloride ions in a mixture of *o*-phenylenediamine and calcium arabonate after it had been condensed indicated a considerable loss of hydrogen chloride during the reaction.

Experimental.

Benziminazoles from Guanosine.—(i) Guanosine (15 g.), prepared from yeast nucleic acid (The Pharmaco-Chemical Products Co. Ltd.) as described by Bredereck, Martini, and Richter (*Ber.*, 1941, **74**, 694), was heated under reflux for 2 hours with N/10-sulphuric acid (2·5 l.). Silver sulphate (20 g.) was added to the hot solution, and next day the precipitate was removed and the solution was freed from silver ions by passage of hydrogen sulphide, filtration, and aeration, and from sulphate ions by addition of hot saturated baryta and filtration from barium sulphate. Analysis (Hinton and Macara, *Analyst*, 1924, **49**, 2) showed the solution to contain 6·45 g. of pentose. After concentration of the solution under reduced pressure to 350 c.c., the pentose was oxidised as described by Hudson and Isbell (*loc. cit.*), and the resulting solution of aldonic acid was refluxed for 3 hours with calcium carbonate. Excess of calcium carbonate was removed, and the filtrate was concentrated under reduced pressure to 20 c.c. and added to 95% ethyl alcohol (350 c.c.). After thorough cooling, the precipitate (7·8 g.) was collected and dried. This calcium aldonate (4 g.) was heated at 130—140° for 2 hours with *o*-phenylenediamine (1·58 mols.), concentrated hydrochloric acid (1·98 mols. of hydrogen chloride), water (8 c.c.), and ethyl alcohol (2 c.c.). The resulting syrup was dissolved in hot water (50 c.c.), decolorised with charcoal, and made alkaline to litmus by addition of 4N-sodium hydroxide (6 c.c.) and a few drops of ammonia (*d* 0·880). After being cooled in the refrigerator, the precipitated arabobenziminazole was collected, and when crystallised from hot water formed needles, m. p. 240—241° not depressed by admixture with synthetic *d*-arabobenziminazole (Found: N, 11·7. Calc. for $C_{11}H_{14}O_4N_2$: N, 11·8%). In 5% aqueous citric acid (*c*, 2·0) $[\alpha]_D^{20°}$ was − 49·5°. Richtmyer and Hudson (*loc. cit.*) give $[\alpha]_D^{20°}$ − 49·4°; Moore and Link (*loc. cit.*) give $[\alpha]_D^{25°}$ − 51°. The picrate had m. p. 158—159° (Found: N, 14·5. Calc. for $C_{11}H_{14}O_4N_2,C_6H_3O_7N_3$: N, 15·0%), and the hydrochloride had m. p. 230—232° (Found: N, 10·2. Calc. for $C_{11}H_{14}O_4N_2,HCl$: N, 10·2%); Moore and Link (*loc. cit.*) give m. p. 158° and 229° respectively.

The filtrate from *d*-arabobenziminazole, after removal of *o*-phenylenediamine by extraction with ether, was evaporated to dryness under reduced pressure. Water (10 c.c.) was added and, after being cooled in ice, the impure *d*-ribobenziminazole was collected and crystallised twice from water from which it separated in needles, m. p. 189—191° not depressed by admixture with synthetic *d*-ribobenziminazole (Found: N, 11·9. Calc. for $C_{11}H_{14}O_4N_2$: N, 11·8%). In 5% aqueous citric acid (*c*, 2·0) $[\alpha]_D^{20°}$ was + 22·0°; Richtmyer and Hudson (*loc. cit.*) give $[\alpha]_D^{20°}$ + 21·6°, and Dimler and Link (*loc. cit.*) give $[\alpha]_D^{20°}$ + 22·5° in N-hydrochloric acid. The picrate had m. p. 184—186° (Found: N, 14·9. Calc. for $C_{11}H_{14}O_4N_2,C_6H_3O_7N_3$: N, 15·0%), and the hydrochloride had m. p. 200—202° (Found: N, 10·2. Calc. for $C_{11}H_{14}O_4N_2,HCl$: N, 10·2%); Dimler and Link (*loc. cit.*) give m. p. 185—186° and 196—198° respectively.

(ii) The previous experiment was repeated exactly using guanosine prepared from yeast nucleic acid supplied by British Drug Houses Ltd. *d*-Arabo- and *d*-ribo-benziminazoles were obtained as before.

(iii) Guanosine from the same sample as that used in experiment (i) was hydrolysed in the same way as before, the sugar solution so obtained was oxidised by the same method, and the calcium aldonate was condensed with *o*-phenylenediamine by the same procedure except that 2·48 mols. of hydrogen chloride were used instead of 1·98. *d*-Ribobenziminazole was isolated, having m. p. 190—191° not depressed by admixture with synthetic *d*-ribobenziminazole; no *d*-arabobenziminazole was obtained.

(iv) Guanylic acid (6·3 g.), prepared according to Buell and Perkins (*J. Biol. Chem.*, 1927, **72**, 21) was heated under reflux for 96 hours with 50% aqueous pyridine (100 c.c.). The solution was then evaporated to dryness under reduced pressure and the residue dissolved in the smallest quantity of hot water. After being thoroughly cooled, the guanosine was crystallised from water, and a sample (3·8 g.) was hydrolysed, the sugar oxidised, and the calcium aldonate condensed with *o*-phenylenediamine exactly as in experiment (iii). *d*-Ribobenziminazole alone was obtained.

(v) Calcium aldonate obtained from guanosine as described in experiment (i) was condensed with *o*-phenylenediamine as in experiment (iii), and yielded only *d*-ribobenziminazole. The same calcium aldonate was then condensed with *o*-phenylenediamine as in experiment (i), but using 1·4 mols. of hydrogen chloride. Both *d*-arabobenziminazole and *d*-ribobenziminazole were isolated and compared with synthetic materials.

Preparation of d-*Ribobenziminazole from Adenosine.*—Adenosine (10 g.), prepared as described by Bredeck, Martini, and Richter (*loc. cit.*) from yeast nucleic acid supplied by The Pharmaco-Chemical Products Co. Ltd., was hydrolysed by the same procedure as that used in experiments with guanosine. The calcium aldonate obtained by oxidising the sugar by the method of Hudson and Isbell (*loc. cit.*) was condensed as already described with *o*-phenylenediamine (1·58 mols.) in presence of hydrogen chloride (2·48 mols.). No arabobenziminazole was isolated. *d*-Ribobenziminazole was obtained having m. p. 190—191°, and did not depress the m. p. of synthetic *d*-ribobenziminazole. In 5% citric acid $[\alpha]_D^{20°}$

was + 21·5°. The picrate and hydrochloride had m. ps. 184—185° and 200—201° respectively, not depressed by admixture with authentic specimens.

Preparation of d-*Ribobenziminazole from Yeast Nucleic Acid.*—(*a*) Yeast nucleic acid (B.D.H.) (40 g.) was refluxed with N/10-sulphuric acid (4 l.) for 6 hours. Colorimetric analysis for inorganic and total phosphate then showed that hydrolysis of the purine nucleotides was complete. Silver sulphate was added to the solution and, after removal of the precipitated silver salts of purines and pyrimidine nucleotides, the filtrate was freed from silver ions by passage of hydrogen sulphide, filtration (charcoal), and aeration, and from sulphate ions by addition of hot saturated baryta and removal of the barium sulphate by filtration. The filtrate, after being concentrated under reduced pressure to 250 c.c., contained 6·2 g. of pentose (Hinton and Macara, *loc. cit.*) and was oxidised as described by Hudson and Isbell, yielding calcium aldonate (6·7 g.). The aldonate (4 g.) was condensed with *o*-phenylenediamine (1·58 mols.) and concentrated hydrochloric acid (2·48 mols. of hydrogen chloride) as previously described. *d*-Ribobenziminazole (1·4 g.) was obtained and had m. p. 190—191° not depressed by admixture with synthetic *d*-ribobenziminazole. The picrate and hydrochloride had m. p. 184—185° and 201—202° respectively, not depressed by admixture with authentic specimens.

(*b*) Repetition of the preceding experiment with yeast nucleic acid supplied by the Pharmaco-Chemical Products Co. Ltd. gave identical results.

(*c*) Yeast nucleic acid (B.D.H.) (50 g.) was refluxed for 4 hours with N-hydrobromic acid (2 l.) and sufficient bromine to saturate the solution. After removal of excess of bromine by distillation, purines, pyrimidine nucleotides, and most of the bromide ions were removed by addition of lead carbonate to the hot solution, which was cooled and filtered from lead bromide. Excess of lead was removed from the filtrate by passage of hydrogen sulphide followed by aeration, and bromide ions were then completely removed by addition of silver carbonate. The filtrate from silver salts was freed from silver with hydrogen sulphide, and, after removal of silver sulphide, the solution was concentrated under reduced pressure to 500 c.c. and refluxed with calcium carbonate for 2 hours. After filtration (charcoal) from excess of calcium carbonate and concentration under reduced pressure to 20 c.c., the solution was poured into 95% ethyl alcohol (500 c.c.). The calcium aldonate was collected and condensed with *o*-phenylenediamine (1·58 mols.) and hydrochloric acid (2·48 mols. of hydrogen chloride) as described above. *d*-Ribobenziminazole was isolated and had m. p. 190—191° not depressed by admixture with synthetic *d*-ribobenziminazole.

Determination of the Loss of Hydrogen Chloride during Condensation.—Calcium *d*-arabonate (4 g.), prepared from *d*(−)-arabinose by oxidation with bromine, was heated at 130—140° for 2 hours with *o*-phenylenediamine (1·48 mols.), concentrated hydrochloric acid (1·3 mols. of hydrogen chloride), water (8 c.c.), and ethyl alcohol (2 c.c.). The syrup was dissolved in water (50 c.c.) and made neutral to litmus by addition of 2N-sodium hydroxide followed by a few drops of aqueous ammonia (*d* 0·880), and after removal of the precipitated arabobenziminazole by filtration the solution was diluted to 60 c.c. and analysed for chloride ions by titration with silver nitrate. The solution contained 0·025 mol. of hydrogen chloride.

It is a pleasure to record our gratitude to Imperial Chemical Industries Ltd. for the loan of equipment.

UNIVERSITY COLLEGE, NOTTINGHAM. [*Received, April 23rd*, 1946.]

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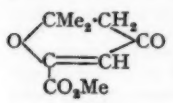
6. *Acid–Base Catalysis in Non-aqueous Solvents. Part X. The Isomerisation of Methyl Mesityl Oxide Oxalate in Chlorobenzene Solution at 99°.*

By R. P. BELL and (MRS.) S. M. RYBICKA.

Measurements are reported on the rate of conversion of the enolic α-form of methyl mesityl oxide oxalate into the cyclic β-form. The reaction is of the first order, catalysed by acids and by bases, and data are given for catalysis by 11 amines and 8 carboxylic acids. The reaction velocity is proportional to the catalyst concentration at low concentrations, but at high concentrations tends to a limiting value which is independent of both the concentration and the nature of the catalyst. This is interpreted by supposing that the α-form is first converted by the catalyst into the isomeric enol, which then changes to the β-form at a rate independent of the catalyst. The effectiveness of catalysts in the first stage of the reaction is closely related to their dissociation constants in water.

THE esters of mesityl oxide oxalic acid were first prepared by Claisen (*Annalen*, 1896, **291**, 132), and various properties of the α- and β-forms were measured by Brühl (*Z. physikal. Chem.*, 1899, **30**, 12). Both these authors assigned the structures CMe_2:CH·CO·CH:C(OH)·CO_2Me and CMe_2:CH·CO·CH_2·CO·CO_2Me to the α- and the β-form respectively. Later, Dieckmann (*Ber.*, 1920, **53**, 1772) called attention to a number of points which do not accord well with the idea of a simple keto-enol tautomerism. In particular, the qualitative observations then available showed that the conversion of the α- into the β-form was always slow, and was catalysed by acids more than by bases; both these points contrast with the known behaviour of simple keto-

enol tautomers. Dieckmann agreed with the above structure for the α-form, but suggested that the β-form is actually (I), and this formulation is now generally accepted, being supported by other chemical evidence (Borsche and Thiele, *Ber.*, 1923, **56**, 2132) and by absorption spectra (Morton and Rogers, *J.*, 1926, 713). The reaction was selected for kinetic study because it is more convenient than the very labile keto-enol changes, and because it offers an opportunity of studying catalysis by amine bases. Although some of these bases have been used extensively as catalysts in preparative organic chemistry, there is practically no quantitative information on their effectiveness as catalysts, since most of the existing kinetic work on basic catalysis deals with anion bases.



(I.)

Experimental.

Materials.—Both forms of methyl mesityl oxide oxalic ester were prepared as described by Claisen (*loc. cit.*). The α-ester was dissolved in dilute sodium carbonate solution and precipitated by a slight excess of dilute acetic acid at 0°: this was repeated several times, and the product recrystallised several times from ligroin (m. p. 84°). The β-ester was dissolved in ether and the solution shaken with sodium carbonate solution to remove any α-ester. After distillation of the ether the β-ester was recrystallised from ligroin (m. p. 67°).

Benzylamine was a pure commercial product. Piperidine, diethylamine, triethylamine, α-picoline and *s*-collidine were dried over solid potassium hydroxide and fractionally distilled. Diethyl-*p*-toluidine was fractionally distilled four times, and nicotine twice under reduced pressure. Diethylaniline was fractionally frozen (m. p. − 34·5°) and then twice redistilled. Benzyldiethylamine was prepared by heating diethylamine and benzyl chloride in a sealed tube: it was dried over solid sodium hydroxide and twice fractionally distilled. Trimethylamine was prepared by warming the hydrochloride with sodium hydroxide solution, and absorbed in chlorobenzene after passage through solid sodium hydroxide. Since the results with this base were anomalous, various methods of purification were tried, including repeated reconversion into the hydrochloride. All samples gave substantially the same kinetic results.

Monochloroacetic, benzoic, and *o*-nitrobenzoic acids were used without further purification. "AnalaR" Acetic acid was four times fractionally frozen (m. p. 15·85°) and then gave kinetic results identical with the original sample. *m*-Nitrobenzoic acid was twice recrystallized from aqueous acetone mixture, and *p*-toluic acid from water. Dichloroacetic acid was fractionally distilled. Trimethylacetic acid was prepared from pinacol (*Org. Synth.*, Coll. Vol. I, p. 512) and dried by distilling it with benzene: it was then fractionated three times in a vacuum.

Chlorobenzene was dried over phosphoric oxide and fractionally distilled: it boiled within 0·2°.

Estimation of the α-Ester.—This was effected by means of the colour reaction with alcoholic ferric chloride solution, which had been used by Knorr and Schubert (*Ber.*, 1911, **44**, 2777) for equilibrium measurements. The colour measurements were carried out with a Hilger "Spekker" absorptiometer, using the green mercury line and micro-cells holding 0·7 c.c. Preliminary experiments showed that the absorption at this wave-length was independent of the excess ferric chloride concentration and of variations in room temperature, and that it remained unchanged over a period of several hours. The colour was destroyed by the presence of amine bases, but was unaffected by carboxylic acids. Even in the presence of amines the colour developed its normal value provided that trichloroacetic acid was present in more than sufficient quantity to neutralise the amine. Calibration with solutions containing known amounts of α-ester and β-ester showed that the drum-reading was directly proportional to the concentration of α-ester in the range 0—0·0015M, and that the concentration could be measured in this range with an error less than 10^{-5}M. In all the kinetic measurements the comparison cell of the absorptiometer contained a solution of the same composition as that being investigated, with the omission of the α-ester.

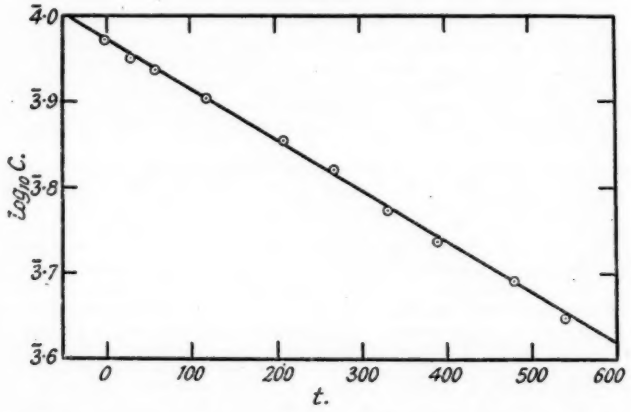
Measurement of Reaction Velocity.—Kinetic measurements were carried out in a steam-bath operating at slightly less than atmospheric pressure. The pressure was regulated by hand to compensate for variations in atmospheric pressure, and the temperature thus maintained at 99° ± 0·1°. The reaction mixture was initially 0·01M with respect to α-ester, and contained the appropriate amount of catalyst in chlorobenzene solution. It was made up by weight, and samples of 0·2—0·5 c.c. transferred by an automatic pipette (Bell, Lidwell, and Vaughan-Jackson, *J.*, 1936, 1792) to 10—12 small glass bulbs, which were then sealed off and placed in the thermostat. Bulbs were removed at intervals, cooled to room temperature, and emptied into weighed tubes containing 1—3 c.c. of 0·006M-ferric chloride in alcohol together with the necessary amount of trichloroacetic acid.

The conversion of α-ester into β-ester does not go quite to completion, experiments with different catalysts indicating 3—8% of α-ester at equilibrium. (Knorr and Schubert, *loc. cit.*, found 3—5% in a number of solvents.) Owing to the slowness of the reaction it is difficult to determine the equilibrium position accurately, and we have therefore preferred to ignore the back-reaction and to study only about the first 60% of the change. Under these conditions a first-order reaction would be anticipated, and in fact a plot of the logarithm of the concentration (or drum-reading) against the time gave a straight line in almost all cases. Fig. 1 gives a typical plot of this kind. The first-order constants given subsequently were obtained graphically, and are defined by $k = 2{\cdot}303\ \mathrm{d}\log_{10}x/\mathrm{d}t$, x being the concentration of α-ester after t minutes. Preliminary experiments showed that the value of k was not appreciably changed by varying the ester concentration by a factor of 2 in either direction. The addition of water up to a concentration of 0·05M was also without effect, and no special precautions were therefore taken to exclude it.

Glass Catalysis.—In the absence of any added catalyst the reaction velocity is very small and not very reproducible. Successive experiments in bulbs with an internal area of about 3·5 sq. cm. gave values of

10^5k = 8·2, 13·2, 5·0, 6·2, 8·1, 6·8, 7·2, 8·1, 9·1, 7·4 (mean 7·9). In a second experiment the surface was increased to 39 sq. cm. by packing with glass capillaries and the mean velocity constant was $7·6 \times 10^{-4}$, while a third experiment with 44 sq. cm. surface gave $k = 9·0 \times 10^{-4}$. These values are approximately proportional to the extent of the glass surface, and the " spontaneous " reaction is thus clearly due to a heterogeneous reaction. It was found that the reaction catalyzed by bases is not measurably affected by increase of surface, and it is therefore possible to correct for the surface reaction by subtracting the " spontaneous " rate from the observed rate in presence of basic catalysts. This correction has been applied to all the velocity constants in Table I, an amount of $2·1 \times 10^{-5}$ per sq. cm. being subtracted from the observed values. This correction was usually only a small fraction of the whole, but for the weakest tertiary amines the surface reaction contributed as much as half the total velocity, and the results for these bases are therefore less reliable.

FIG. 1.



Catalysis by Bases.—The data obtained are given in Table I, and Fig. 2 shows the dependence of velocity on catalyst concentration for some of the tertiary bases. The slope of the plots falls off rapidly

TABLE I.

Catalysis by bases.

Triethylamine : k_e 0·142; k_∞ = 0·0102.

10^4c	32	87	109	127	170	188	196	230	349	372	414	618	630	944
10^5k obs.	44	104	123	160	220	235	271	247	332	353	360	470	440	584
10^5k calc.	44	110	135	154	196	213	220	248	335	357	374	473	478	581

Trimethylamine : k_e = 0·206; k_∞ = 0·0175.

10^4c	92	460	806	868	884	927	1830
10^4k obs.	17	58	88	97	100	108	119
10^4k calc.	17	62	86	89	89	91	120

Benzyldiethylamine : k_e = 0·0118; k_∞ = 0·0067.

10^3c	48	95	191	343
10^5k obs.	53	95	146	257
10^5k calc.	52	96	168	251

Nicotine : k_e = 0·0078; k_∞ = 0·0100.

10^3c	46	92	132	137
10^5k obs.	36	63	92	93
10^5k calc.	28	67	94	97

s-Collidine : k_e = 0·0021.

10^3c	49	100	198
10^5k (obs.)	9	16	23
$10^4k/c$	18	16	12

Diethyl-p-toluidine : k_e = 0·00086.

10^3c	100	200	302
10^6k (obs.)	73	105	128
$10^5k/c$	73	52	43

Diethylaniline : k_e = 0·00036.

10^3c	90	270	452
10^5k (obs.)	3	7	9
$10^5k/c$	33	26	20

α-Picoline : k_e = 0·00046.

10^3c	91	183	325
10^5k(obs.)	4	5	8·5
$10^5k/c$	44	27	26

Piperidine : k_e = 0·497.

10^4c	44	89	135	152
10^5k(obs.)	210	401	579	637
$10^5k/c$	474	452	428	420

Diethylamine : k_e = 0·234.

10^4c	150	303	604	920
10^4k (obs.)	32	57	91	136
$10^5k/c$	215	187	151	148

Benzylamine : k_e = 0·057.

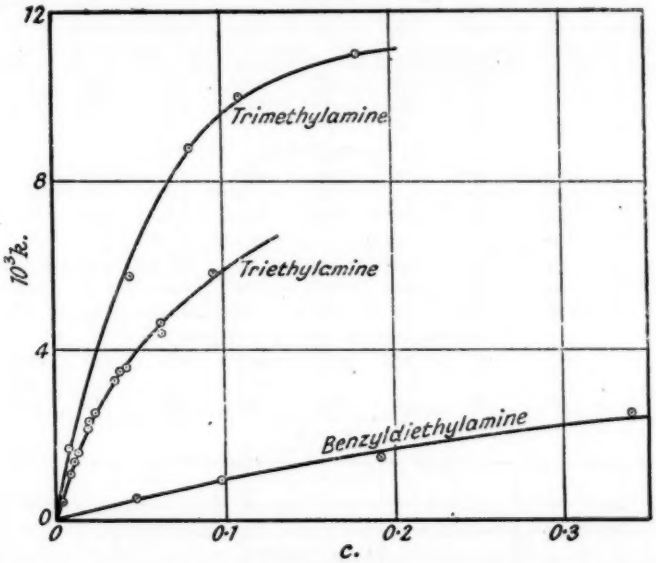
10^4c	151	333	566	903
10^4k (obs.)	7·7	17	28	46
$10^5k/c$	56	54	51	50

with increasing concentration, and the reaction velocity approaches a limiting value at high concentrations of base. This can be expressed by the equation

$$k = k_e k_\infty c/(k_\infty + k_e c) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where c is the base concentration, k_e the catalytic constant in very dilute solutions, and k_∞ the limiting velocity at high concentrations. In the case of triethylamine, trimethylamine, benzyldiethylamine and nicotine the values of k(calc.) are derived from this equation, the values of k_e and k_∞ being given at the head of the data for each base. The weaker tertiary amines *s*-collidine, diethyl-*p*-toluidine, diethylaniline, and α-picoline also show a decrease of catalytic constant with increasing concentration, but the practicable concentration range is not great enough to obtain the limiting velocity or to apply equation (1). For these four amines, therefore, the observed values of k/c were plotted against c, and k_e obtained by extrapolating to $c = 0$.

FIG. 2.



The position is less simple for the primary and secondary amines, since they undoubtedly condense with the ester under our experimental conditions. However, it seemed possible that the condensation was preceded by the catalysed conversion of the α- into the β-ester, or to some intermediate involved in the conversion into β-ester, so that the rate of disappearance of the α-ester would be comparable with its rate of isomerisation in presence of tertiary bases. (It will be shown in the discussion that this supposition was justified.) Since the primary and secondary amines are removed by condensation, the reactions are no longer of the first order, but they do not depart from this as much as might be expected, probably because the condensation products (of the Schiff's base type) also act as catalysts. The velocity constants given in the table represent the initial slopes of the first-order plots, and the values of k_e were obtained by extrapolating to $c = 0$ the plot of k/c against c.

Catalysis by Acids.—In most respects this resembled catalysis by tertiary bases, but a new surface phenomenon appears at low acid concentrations. For example, with solutions of dichloroacetic acid between 0·2 and 0·001M the observed velocity constant fell off steadily but slowly with decreasing concentration, but on decreasing the concentration below 0·001M the velocity decreased rapidly, and became almost zero for concentrations below 0·0003M. It is believed that this behaviour is due to the adsorption of acid on the glass surface, thus reducing the effective catalyst concentration. This view was confirmed by an experiment with 0·001M-dichloroacetic acid in which the glass surface was increased ten-fold by packing with glass capillaries: the effect was to decrease the velocity constant from 8×10^{-3} to 7×10^{-4}. We have therefore assumed that in each unpacked bulb the acid concentration is diminished by adsorption by an amount $3{\cdot}4 \times 10^{-4}$M, and the values of c(corr.) in Table II were obtained

TABLE II.

Catalysis by acids.

Dichloroacetic acid: $k_e = 25$; $k_\infty = 0{\cdot}0145$; $A = 0{\cdot}07$.

10^4c(corr.)	7·2	7·7	15·2	22·7	37·6	89	417	774	879	1823
10^4k obs.	84	81	106	115	126	138	184	200	210	258
10^4k calc.	81	83	105	116	126	141	172	198	205	272

o-Nitrobenzoic acid: $k_e = 11{\cdot}5$; $k_\infty = 0{\cdot}0143$.

10^5c(corr.)	135	219	239	388	802
10^4k obs.	72	97	100	108	124
10^4k calc.	74	91	94	108	124

TABLE II—*contd.*

Monochloroacetic acid: $k_e = 7{\cdot}87$; $k_\infty' = 0{\cdot}0125$; $A = 0{\cdot}027$.

10^4c(corr.)	16·1	35·9	89	94	176	330	895	902	1804
10^4k obs.	63	86	105	107	115	128	150	152	170
10^4k calc.	63	87	106	107	119	128	147	147	173

m-*Nitrobenzoic acid:* $k_e = 7{\cdot}12$; $k_\infty = 0{\cdot}0125$.

10^4c(corr.)	20·5	21·9	31·7	46·4	71	97	197	495
10^4k obs.	71	66	83	91	95	109	113	131
10^4k calc.	67	70	81	91	100	106	115	121

Benzoic acid: $k_e = 2{\cdot}51$; $k_\infty = 0{\cdot}0138$.

10^4c(corr.)	34	49	69	359	902	1806
10^4k obs.	52	62	79	113	129	142
10^4k calc.	53	65	77	120	130	134

p-*Toluic acid:* $k_e = 2{\cdot}44$; $k_\infty = 0{\cdot}0125$.

10^4c(corr.)	33	39	69	89	123	176	720
10^4k obs.	48	66	72	77	88	98	132
10^4k calc.	49	54	72	80	88	97	117

Acetic acid: $k_e = 1{\cdot}07$; $k_\infty = 0{\cdot}0133$.

10^4c(corr.)	34	90	183	368	936	951	1735
10^4k obs.	29	53	81	92	116	120	127
10^4k calc.	29	56	79	100	118	118	125

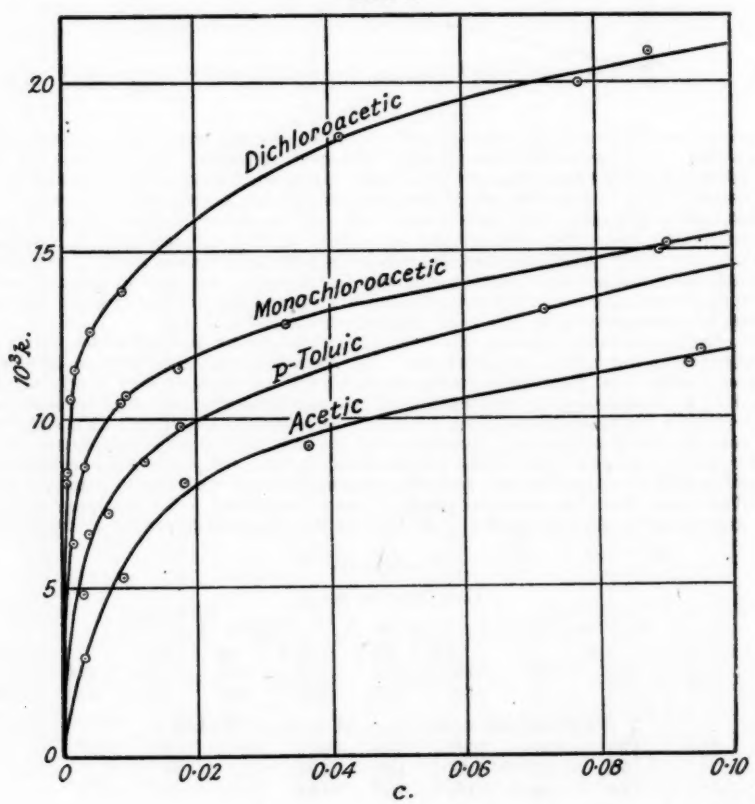
Trimethylacetic acid: $k_e = 2{\cdot}25$; $k_\infty = 0{\cdot}0132$.

10^4c(corr.)	34	86	89	93	98	184	441	924	1885
10^4k obs.	49	80	85	79	79	96	117	120	130
10^4k calc.	48	78	79	81	82	102	116	124	128

Trimethylacetic acid + pyridine.

10^4c(acid)	37	45	45	927	906	904	907	1165
10^4c(base)	0	11	215	0	109	215	323	326
10^4k(obs.)	49	56	56	120	125	139	153	163

FIG. 3.



by subtracting this amount from the stoicheiometric concentrations. Since each bulb contained 0·45 c.c. of solution and had an internal surface of 3·5 sq. cm., this corresponds to about 3×10^{16} molecules per sq. cm. This figure is not unreasonable, since the true surface of the glass is probably considerably greater than its geometrical area, and carboxylic acids are known to be strongly adsorbed from the vapour phase by glass at temperatures near 100°.

The dependence of reaction velocity on catalyst concentration resembled that found for the stronger bases, and typical plots are shown in Fig. 3. However, with monochloro- and dichloro-acetic acids the velocity did not quite reach a limiting value at high concentrations, but continued to increase slowly with increasing concentration. This can be expressed by adding a linear term to equation (1), giving

$$k = k_c k_\infty c/(k_\infty + k_c c) + Ac \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The linear term was not necessary for the weaker acids, or for those which were insufficiently soluble for high concentrations to be studied.

Catalysis in Mixtures of Acid and Base.—The data given at the end of Table II show that the addition of pyridine has no effect on catalysis by trimethylacetic acid. (Pyridine is too weak a base to have a measurable catalytic effect alone.) This contrasts with the often-quoted observations of Richards and Lowry (*J.*, 1925, **127**, 1385) for the mutarotation of tetramethylglucose in mixtures of pyridine and cresol, and offers no support for the view that the interconversion of keto-enol isomers takes place by a simultaneous reaction of both acid and base with the substrate.

Discussion.

The particular feature of this reaction, common to both basic and acidic catalysis, is the fact that the reaction velocity is proportional to the catalyst concentration only at very low concentrations, and approaches a constant limiting value at high concentrations. This behaviour can be best explained by the following reaction scheme.

Let X be the α-ester, Z the β-ester, C the catalyst, and Y some intermediate form of the ester present only in very small concentration. If the reaction takes place in two consecutive steps

$$X + C \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Y + C, \quad Y \xrightarrow{k_2} Z$$

then the conditions for a stationary concentration of Y give

$$k = -\frac{1}{[X]}\frac{d[X]}{dt} = \frac{k_1 k_2 [C]}{k_2 + k_{-1}[C]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

which is identical with equation (1) if we write $k_1 = k_c$, $k_1 k_2 / k_{-1} = k_\infty$. Moreover, since both k_2 and the ratio k_1/k_{-1} are independent of the catalyst, the value of k_∞ should be the same throughout. This is borne out by the experimental data, since although the effectiveness of the eight acid catalysts at low concentrations varies by a factor of 25, the extreme values of k_∞ are 0·0125 and 0·0145. For basic catalysts the data are less satisfactory, since it was only possible to evaluate the maximum rate for triethylamine (0·0102), trimethylamine (0·0175), benzyldiethylamine (0·0067), and nicotine (0·0100), and these values are of low accuracy. However, they show no trend with basic strength and are close to the limiting value for acid catalysis, so that there is substantial evidence for the above reaction scheme.

The intermediate Y is probably the isomeric enol ester, formed from the α-ester by mechanisms resembling those for other prototropic changes, *i.e.*

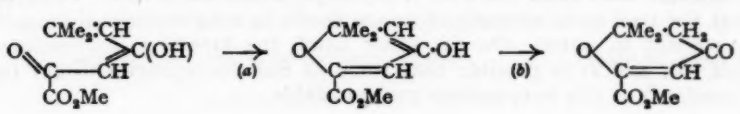
Basic catalysis:

$$\begin{aligned} & CMe_2{:}CH{\cdot}CO{\cdot}CH{:}C(OH){\cdot}CO_2Me + B \\ \rightleftharpoons\ & \left\{\begin{array}{l} CMe_2{:}CH{\cdot}CO{\cdot}CH{:}C(O^-){\cdot}CO_2Me \\ CMe_2{:}CH{\cdot}C(O^-){:}CH{\cdot}CO{\cdot}CO_2Me \end{array}\right\} + BH^+ \\ \rightleftharpoons\ & CMe_2{:}CH{\cdot}C(OH){:}CH{\cdot}CO{\cdot}CO_2Me + B \\ & \qquad (Y) \end{aligned}$$

Acid catalysis:

$$\begin{aligned} & CMe_2{:}CH{\cdot}CO{\cdot}CH{:}C(OH){\cdot}CO_2Me + HA \\ \rightleftharpoons\ & \left\{\begin{array}{l} CMe_2{:}CH{\cdot}C(OH^+){\cdot}CH{:}C(OH){\cdot}CO_2Me \\ CMe_2{:}CH{\cdot}C(OH){:}CH{\cdot}C(OH^+){\cdot}CO_2Me \end{array}\right\} + A^- \\ \rightleftharpoons\ & CMe_2{:}CH{\cdot}C(OH){:}CH{\cdot}CO{\cdot}CO_2Me + HA \\ & \qquad (Y) \end{aligned}$$

where the brackets { } indicate mesomeric ions with a charge distribution intermediate between those represented by the two formulæ. The enol Y thus formed can then pass into the β-ester by the steps



Step (*a*) involves only a bond shift, but it demands a special configuration of the molecule and is likely to be a slow reaction. Step (*b*) is a simple enol-keto change which would be expected to take place rapidly under our experimental conditions. It may be noted that in both the open-chain enols and in the enol and the keto-ring compound all the double bonds form part of a conjugated system. This is not so for the open-chain keto-form, which may account for its non-occurrence.

This scheme explains why the formation of β-ester is much less facile than a simple keto-enol tautomerism, and also why there is greater equality between the catalytic effects of acids and bases, since the mechanism given above for acid catalysis cannot operate in a simple keto-enol change. The slight increase in rate at high concentrations of strong acids [represented by the linear term in equation (2)] is probably due to the attachment of a proton to one of the basic oxygen atoms in the enol Y: this would no doubt affect the rate of ring closure, though it is difficult to predict whether an increase or a decrease is to be expected.

According to the above interpretation, the values of k_e represent the catalytic constants of acids and bases for the interconversion of the two open-chain enols by a prototropic mechanism. It is therefore of interest to compare these catalytic constants with the dissociation constants of the catalysts in water, since it has been shown (Griffiths, *J.*, 1938, 818) that the strengths of acids and bases in chlorobenzene run parallel with those in water. For the bases, values are only available at 25°, and these are given in Table III, while Fig. 4 shows a plot of $\log_{10}k_e$ against $\log_{10}K_d$.

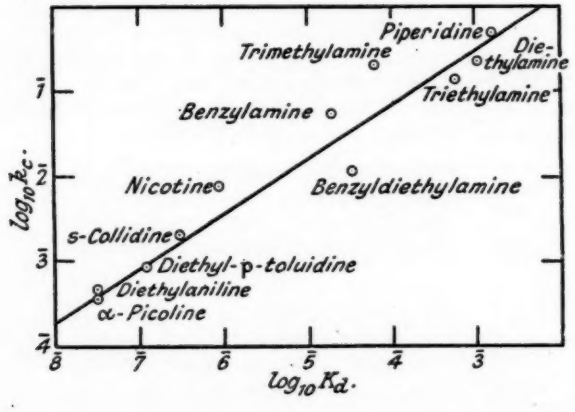
TABLE III.

Catalytic power and basic strength.

Catalyst.	k_e (99°).	K_d (25°).	Ref.	Catalyst.	k_e (99°).	K_d (25°).	Ref.
Piperidine	0·497	$1·6 \times 10^{-3}$	(1)	Nicotine	0·0078	9×10^{-7}	(5)
Diethylamine	0·234	$1·1 \times 10^{-3}$	(2)	*s*-Collidine	0·0021	$2·1 \times 10^{-7}$	(6)
Triethylamine	0·142	$5·9 \times 10^{-4}$	(3)	Diethyl-*p*-toluidine	0·00086	$1·2 \times 10^{-7}$	(2)
Trimethylamine ...	0·206	$6·5 \times 10^{-5}$	(4)	Diethylaniline	0·00036	$3·0 \times 10^{-8}$	(2)
Benzyldiethylamine	0·0118	$3·3 \times 10^{-5}$	(2)	α-Picoline	0·00046	$3·0 \times 10^{-8}$	(7)
Benzylamine	0·057	$2·2 \times 10^{-5}$	(2)				

References for dissociation constants: (1) Bredig, *Z. physikal. Chem.*, 1894, **13**, 191. (2) Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469. (3) Winmill and Moore, *J.*, 1912, 1635. (4) Everett and Wynne-Jones, *Proc. Roy. Soc.*, 1944, **177**, *A*, 499. (5) Craig and Nixon, *J. Amer. Chem. Soc.*, 1931, **53**, 4370. (6) Lunden, *J. Physical Chem.*, 1907, **5**, 574. (7) Constam and White, *Amer. Chem. J.*, 1903, **5**, 574.

FIG. 4.



It will be seen that there is a rough linear relation between these two quantities, the slope of the straight line in the figure being 0·66. The most serious discrepancy is for trimethylamine, and it is of interest that other workers (Brown, *J. Amer. Chem. Soc.*, 1944, **66**, 431) have concluded that the true basic strength of this molecule is not satisfactorily represented by its dissociation constant in water. On the other hand, the kinetic measurements relate to a temperature of 99°, and it is possible that some of the discrepancies would be removed if dissociation constants at this temperature were available.

The primary and secondary amines fall well on the same straight line as the tertiary amines. This confirms the view that their condensation reaction with the ester involves a prototropic change and is kinetically allied to the transformation of α-ester into β-ester. Since for these amines the initial rate is roughly proportional to the amine concentration, it seems likely that the condensation takes place rapidly with the intermediate enol isomer $CMe_2{:}CH{\cdot}C(OH){:}CH{\cdot}CO{\cdot}CO_2Et$, in which the carbonyl group would be especially reactive.

For most of the acid catalysts, dissociation constants in water at 100° are either directly available or can be estimated by extrapolation. Table IV and Fig. 5 show how the dissociation constants at 25° and 100° compare with the observed values of k_c.

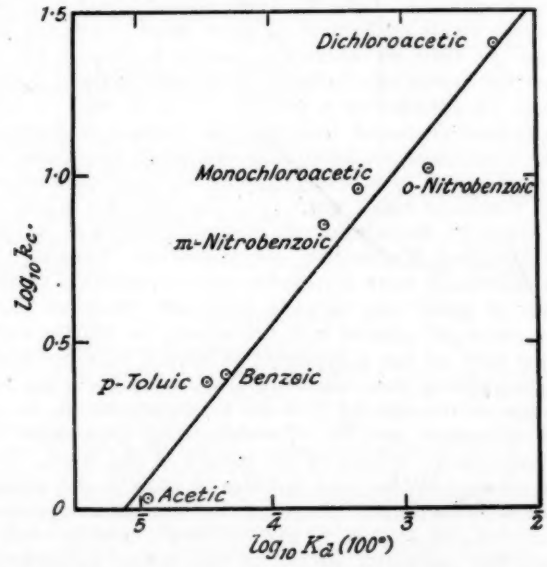
TABLE IV.

Catalytic power and acid strength.

Acid.	k_c.	K_d. 25°.	K_d. 100°.	Ref.
Dichloroacetic	25	$5{\cdot}1 \times 10^{-2}$	$5{\cdot}0 \times 10^{-2}$	(1)
o-Nitrobenzoic	11·5	$6{\cdot}3 \times 10^{-3}$	$1{\cdot}6 \times 10^{-2}$	(2)
Monochloroacetic	7·87	$1{\cdot}38 \times 10^{-3}$	$4{\cdot}7 \times 10^{-3}$	(3)
m-Nitrobenzoic	7·12	$3{\cdot}4 \times 10^{-4}$	$2{\cdot}6 \times 10^{-3}$	(2)
Benzoic	2·51	$6{\cdot}6 \times 10^{-5}$	$4{\cdot}5 \times 10^{-5}$	(2)
p-Toluic	2·44	$4{\cdot}3 \times 10^{-5}$	$3{\cdot}3 \times 10^{-5}$	(2)
Acetic	1·07	$1{\cdot}75 \times 10^{-5}$	$1{\cdot}11 \times 10^{-5}$	(4)
Trimethylacetic	2·25	$9{\cdot}1 \times 10^{-6}$	—	(5)

References for dissociation constants : (1) Ostwald, *Z. physikal. Chem.*, 1889, **3**, 177. Value at 100° extrapolated from kinetic data (Baughan and Bell, *Proc. Roy. Soc.*, 1937, **156**, *A*, 464). (2) Schaller, *ibid.*, 1898, **25**, 519. (3) Wright, *J. Amer. Chem. Soc.*, 1934, **56**, 314 (100° value extrapolated). (4) Noyes, *ibid.*, 1904, **30**, 318. (5) Dippy, *J.*, 1938, 1222.

FIG. 5.



It will be seen that there is a fairly close relation between the catalytic constants at 99° and the dissociation constants at 100°, the slope of the line in Fig. 5 being 0·49. If dissociation constants at 25° are used the agreement is somewhat less satisfactory, and a serious discrepancy is shown by trimethylacetic acid : unfortunately, the dissociation constant of this acid is only known at a single temperature (25°).

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UNIVERSITY PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, April 24th*, 1946.]

7. *The Catechins of Green Tea. Part I.*

By A. E. Bradfield, (Miss) M. Penney, and (in part) (Miss) W. B. Wright.

From the polyphenol fraction extracted from a green-tea infusion by ethyl acetate, *l*-gallocatechin and a *substance*, $C_{15}H_{14}O_7,H_2O$, probably *dl*-gallocatechin, have been isolated by partition chromatography.

Two flavonols, quercetin, present as a glycoside (Hlasiwetz and Malin, *Jahresber.*, 1867, 732; Deuss, *Rec. Trav. chim.*, 1923, **42**, 623), and kaempferol (Oshima and Ka, *Bull. Agric. Chem. Soc. Japan*, 1936, **12**, 133), have been isolated from green tea. Early work on the more characteristic polyphenols extractable by ethyl acetate from aqueous infusions of fresh green tea leaf or of green tea—the so-called " white tannin " of tea—indicated in addition to small amounts of gallic acid (Hlasiwetz, *Annalen*, 1867, **142**, 233) the presence of " condensed tannins," and occasionally small amounts of crystalline material were obtained (Deuss, *Meded. K. Proefstaat vor Thee*, 1914, 31; Shaw, *United Planters' Assoc. S. India*, Bull. No. 4, 1935). More recently, by fractionation of the ethyl acetate extract of Japanese green tea, Tsujimura has isolated in low yield *l-epi*catechin (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1929, **10**, 253), *l*-gallocatechin (*ibid.*, 1934, **24**, 149), and 3-galloyl*epi*catechin (*ibid.*, 1930, **14**, 63; 1935, **26**, 186; 1931, **15**, 155). *epi*Catechin and gallocatechin have also been obtained from Formosan tea (Oshima, *Bull. Agric. Chem. Soc. Japan*, 1936, **12**, 103; Oshima and Goma, *J. Agric. Chem. Soc. Japan*, 1933, **9**, 948).

In all of six specimens of Java leaf examined by Deijs (*Rec. Trav. chim.*, 1939, **58**, 805), *epi*catechin and its 3-galloyl ester were present, but gallocatechin could only be obtained from three of the samples. In Ceylon leaf, gallocatechin has been reported (Lamb, *Tea Quart.*, 1938, **11**, 103). In addition to these crystalline substances,* all workers have encountered a considerable proportion of amorphous material, shown by Deijs (*loc. cit.*) to be a mixture and to contain combined gallic acid liberated in high yield by tannase, or less efficiently by acid hydrolysis. Harrison and Roberts (*Biochem. J.*, 1939, **33**, 1408) also find that prolonged hydrolysis of " tea tannin " from Indian tea yields gallic acid in some cases. On the other hand, Lamb and Sreerangachar (*Biochem. J.*, 1940, **34**, 1472) were unable to observe the liberation of gallic acid when *Aspergillus niger* was grown on a solution of an amorphous " tannin " from Ceylon leaf. In no case could sugars be detected as a product of either acid or enzymic hydrolysis. By reduction of the appropriate chalkone, following the method of Russell and Todd (*J.*, 1934, 1066), Oshima (*loc. cit.*) obtained an amorphous material, formulated as bis-(5 : 7 : 3′ : 4′ : 5′-pentahydroxy)flavpinacol, which he considered to be identical with an amorphous preparation obtained by him from Formosan tea. Apart from the difficulty of establishing the identity of amorphous powders, Russell's formulation of similar products as flavpinacols has been very strongly criticised (Freudenberg, Karimullah, and Steinbrunn, *Annalen*, 1935, **518**, 37).

In an attempt to determine more completely the composition of the polyphenol mixture present in an infusion of green tea, use has now been made of the method of partition chromatography on a silica gel column first introduced by Martin and Synge (*Biochem. J.*, 1941, **35**, 1358). Some 80% of the polyphenol extracted by ethyl acetate is soluble in wet ether, and by chromatographing this solution gallocatechin is readily separated in a yield of about 1·3% of the weight of the tea (8·5% of the total polyphenol), *i.e.*, about 4—5 times the yield obtained by Tsujimura's method. Corresponding to another well-marked band, a *substance* (*B*) is obtained (yield: 0·55% of the weight of tea, 3·6% of the total polyphenol), which separates from aqueous alcohol as a mixture of rhombs and minute needles in variable proportions, with no definite decomposition point, and has the composition $C_{15}H_{14}O_7,H_2O$. It yields an *acetyl* derivative $C_{27}H_{26}O_{13}$, m. p. 158·5—159·5°, isomeric with that of gallocatechin. Attempts to determine the molecular weight of this acetyl compound and to confirm the molecular weight of gallocatechin acetate by Rast's method were at first unsuccessful, owing to decomposition of the substances in the camphor solution. It was found that by raising the temperature fairly rapidly and making single observations on fresh specimens of the mixture, consistent results could be obtained, but although under these conditions no visible browning occurred, it was not felt that complete reliance could be placed on the calculated molecular weights. Recourse was therefore made to the *X*-ray method. The minute hair-like needles of the acetate of substance *B* were unsuitable for study, but for the molecular weight of the parent

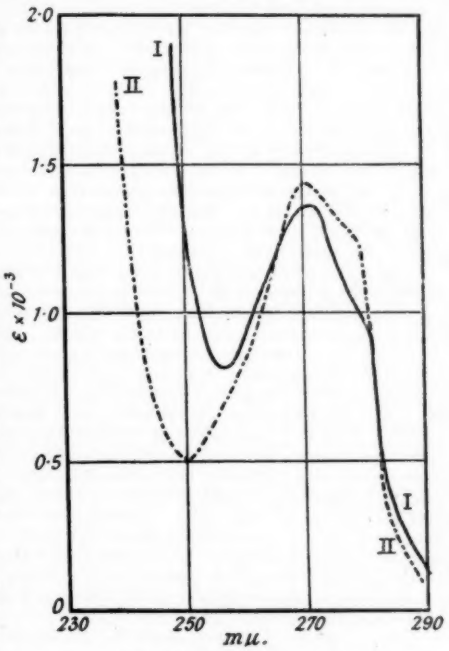
* Nierenstein (*Analyst*, 1936, **61**, 294) states that green Assam tea contains a crystalline substance, of which the crystalline methyl ether on hydrolysis yields 1 molecule of tetramethylacacatechin, 2 molecules of 3 : 4-dimethylgallic acid, and 1 molecule of trimethylgallic acid. No details are given.

substance a value of 324 ± 5 was obtained, in agreement with the value 324 calculated for $C_{15}H_{14}O_7,H_2O$. It is not yet possible to say whether this substance is a monohydrate or whether the water is present in the constitution and is eliminated in the formation of the acetyl derivative. A similar *X*-ray study of the crystals of gallocatechin acetate completely confirms the molecular weight of this substance.

The substance *B* is less soluble in water, alcohol and moist ether than gallocatechin, very sparingly soluble in dry ether, and insoluble in chloroform and hydrocarbons. It gives the pine-shaving test for phloroglucinol and, like gallocatechin, it gives with ferric ion in alcoholic solution an intense blue colour, fading slowly, and in aqueous solution a blue-black colour fading to colourless in a second or two; with sodium cyanide solution it gives a reddish-orange colour which fades and is restored by shaking the tube. The absorption spectra of the substance and its acetyl derivative (see fig.) are practically identical with those of gallocatechin and hexa-acetyl gallocatechin respectively. The substance is optically inactive in alcohol and in water–acetone (1 : 1) and is probably the *dl*-form of gallocatechin or its epimer. The investigation of this substance is being continued.

The remaining polyphenol fractions incompletely separated by the procedure now described may be resolved by a modification employing a different solvent. These fractions are under examination and their separation and properties will be described later. It may be mentioned that, as reported by other workers (Martin and Synge, *loc. cit.*; Gordon, Martin, and Synge, *Biochem. J.*, 1944, **38**, 65; Bell, *J.*, 1944, 473), some difficulty was at first experienced in obtaining results reproducible with different batches of silica. A satisfactory method of preparation of the gel is described in the Experimental part.

For purposes of identification, the optical characteristics, so far as they could be obtained, of the crystals of substance *B*, gallocatechin, and their respective acetates, and the interplanar spacings calculated from Debye–Scherrer photographs of the four substances are given below.



I. *Substance B.*
II. *Acetate of substance B.*

Experimental

(Microanalyses are by Drs. Weiler and Strauss, Oxford.)

Preparation of Silica Gel.—The volume (*n* c.c.) of concentrated hydrochloric acid required to neutralise the quantity of sodium silicate taken for the preparation described below was first determined by titration (methyl-orange) of the water-glass (*d* 1·42; 30 g.) diluted with water (500 c.c.). For the preparation, water-glass (210 g.) was diluted with water (300 c.c.) and concentrated hydrochloric acid (volume equal to 0·38*n*) run in from a burette in a continuous stream with vigorous stirring. Stirring and addition of acid were stopped immediately the solution thickened, and it rapidly set to a clear gel containing some opaque flecks, becoming in a few minutes entirely opaque. After being left for one hour from the time stirring was stopped, the stiff gel was broken up with a stirring rod, and during the next 35 minutes a volume of hydrochloric acid equal to 0·57*n* was added in 1-c.c. portions (total hydrochloric acid = 0·95*n*). The mixture was set aside for 3 hours, filtered through a Buchner funnel, and washed thoroughly without allowing the surface of the gel to crack. The gel was transferred to a beaker with water (200 c.c.) and after ageing for 24 hours, was filtered off, well washed, drained with suction for 30 minutes, and dried at 110—120°. The dried gel was stirred with concentrated hydrochloric acid (250 c.c.). After 30 minutes, water (250 c.c.) was added, and the gel was filtered off and well washed. Treatment with hydrochloric acid (150 c.c.) was repeated. After being filtered off and washed, the gel was stirred with boiling water (200 c.c.) for 10 minutes, cooled, filtered off, drained for 30 minutes, and dried at 110—120°. The product was ground and sifted to pass a 120-mesh (aperture 0·124 mm.) sieve and re-dried (yield ~ 50 g.). For the preparation of a gel with reproducible properties, attention is directed to the necessity of strict standardisation of the method of precipitation with acid, as well as of after-treatment.

Silica gel which has been used for chromatographic separation of tea polyphenols may be purified and used repeatedly. Solvent from material from the columns was removed in the steam-oven, the gel suspended in dilute sulphuric acid, and excess aqueous permanganate added. After 15 minutes the

suspension was decolorised with sulphur dioxide, filtered, and the gel washed. It was further treated once with hydrochloric acid, then with boiling water, dried, sifted, and re-dried as for new silica.

Chromatographic Procedure.—For the columns, a glass tube 3·15 cm. in internal diameter and 40—45 cm. long rested on a perforated nickel or silver disc, covered with filter-paper, in an adapter, the lower portion of which had a stopcock and was drawn out to a jet of about 2 mm. internal diameter. The upper portion of the glass tube was closed with a rubber bung carrying a 250-c.c. separating funnel, with the stem drawn out to a jet curved to touch the inside wall of the tube. Appropriate connections were also made for applying air pressure from an aspirator to the column. A thin cardboard scale was clamped behind the tube to facilitate the determination of the rate of flow of solvent. Silica gel (40 g.) was mixed with water (26 c.c.), suspended in wet, peroxide-free ether (200 c.c.), and the slurry poured into the tube, further small quantities of ether being required to complete the transfer. The silica was allowed to settle, wet ether flowing through the column without additional pressure. After ½ hr., air pressure from the aspirator was applied and adjusted to give the desired rate of flow (pressure 20—40″ of water). Occasional tapping assisted the column to settle down. When solvent had been flowing through the column under pressure for approximately 45 minutes, the space above the gel was filled to a depth of 15 cm. with ether, and the upper part of the gel lightly stirred to level the surface, and this quantity of ether allowed to flow through under pressure until the depth was about 1 mm. The polyphenol solution was then poured in through a funnel, made by drawing out a 1-cm. wide tube to a long capillary, held touching the inner wall of the tube. The solution and the first 50 c.c. of developing solvent (wet, peroxide-free ether) were allowed to flow through at a rate of 150 c.c./hr. (pressure 8—12″ of water). For the remainder of the development the rate of flow was increased to 350—400 c.c./hr. (pressure 20—30″ of water). Both during the settling down period and during working, patches occasionally appear where the gel has the appearance of drying locally. If neglected, these patches develop into cracks in the column. Local cooling by wrapping cotton wool moistened with ether round the outside of the tube (or the adapter) will cause these patches to disappear in 5—15 minutes, without interfering with the working of the column.

Under the conditions employed, the colourless bands were successively eluted and were detected by collecting four drops of the eluate in a test-tube every five minutes, and adding 2—3 c.c. of water and one drop of a *p*-nitrobenzenediazonium chloride solution (M/3), yellow to brownish-orange colours developing when polyphenol was present in the eluate. By timing additions of solvent to the column, the volumes of developing solvent corresponding to the appearance in the eluate of the beginning and the end of each band could be obtained from the times of the tests.

Extraction of Green-tea Polyphenols.—Distilled water (250 c.c.) and Ceylon tea (10 g.) were brought to the boil, maintained at the boiling point for 5—6 minutes, cooled, and filtered through muslin. The infusion (200 c.c.) and chloroform (150 c.c.) were refluxed for 15 minutes, cooled, and transferred to a separating funnel by pouring through a thistle-funnel reaching to the bottom (to avoid emulsification). After separation of the layers, extraction was completed in a continuous-extraction apparatus for 6—8 hours. Chloroform removes caffeine, some chlorophyll degradation products, and traces of carotenoid pigments from the infusion. The aqueous solution was separated, boiled for a few minutes while a current of carbon dioxide was passed through it to remove chloroform, and continuously extracted with ethyl acetate (12 hours). From the ethyl acetate extract the solvent was distilled off in a current of carbon dioxide, the latter portion under diminished pressure. The residue was washed into a dish with acetone, which was evaporated on the water-bath. The resinous residue broke up to a light brownish-orange amorphous powder (1·25 g.).

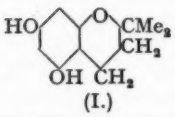
Chromatogram of Ether-soluble Polyphenols.—The orange powder obtained as above (2·0 g.) was rubbed with successive portions of wet ether (total volume 40 c.c.), and the solution, decanted from the insoluble portion (0·4 g.), chromatographed as described above. A barely visible pale green band passed rapidly down the column and appeared as a green solution in the eluate. It was rapidly followed by several incompletely separated polyphenol bands, the whole eluate from approximately 60 c.c. to 600 c.c. being collected as fraction (*a*). After a clear space, a well-defined band was collected as fraction (*b*), and a following band as fraction (*c*) (corresponding to the passage of approximately 700 to 1000 c.c. and 1200 to 1800 c.c. of solvent, respectively). During development, faintly coloured bands moved very slowly down the column. At the end, a narrow pink band was just visible 2—3 cm. from the top. Somewhat lower was a broad, faintly yellow band. These were not investigated. Fraction (*a*) was dried ($MgSO_4$), concentrated by distillation in a current of carbon dioxide, transferred to a dish, evaporated to dryness in a carbon dioxide stream at room temperature, and kept for later examination (1·07 g.). Fraction (*b*): The combined solutions from two columns were dried ($MgSO_4$) and concentrated by distillation in carbon dioxide to 30 c.c. A portion of the material crystallised out on standing. The remainder was obtained after rechromatographing the decanted solution on 40 g. of silica mixed with 26 c.c. of water. The eluate containing the required fraction was dried and evaporated to dryness as described for fraction (*a*); yield 0·14 g. from 4 g. of orange powder. Fraction (*c*) was dried, concentrated to 30 c.c., and rechromatographed from 40 g. of silica. When the band appeared in the eluate the next 150 c.c. of the eluate were discarded before the main portion was collected. Solvent was removed as described above. Yield 0·17 g. from 2 g. of the orange powder.

Substance B.—The fraction (*b*) (0·1 g.) was dissolved in water–alcohol (2 : 1 by vol.; 3 c.c.) at 70°, and the *substance* separated on cooling as a mixture of white rhombs and minute needles, the former usually predominating. Conditions were not found for obtaining either form exclusively. After drying over sulphuric acid, a specimen consisting mainly of needles decomposed in the neighbourhood of 160°, whereas a largely rhombic specimen decomposed at about 195°. In all specimens the decomposition point was far from sharp. No further loss in weight occurred on drying in a high vacuum at room temperature. At higher temperatures decomposition ensued; $[\alpha]_D^{20°} \pm 0·0°$ ($c = 0·37$, in alcohol; 0·42, in water–alcohol, 1 : 1 by vol.) (Found: C, 55·9; H, 5·08. $C_{15}H_{14}O_7,H_2O$ requires C, 55·6; H, 4·97%). Its *acetyl* derivative crystallised from dilute acetic acid in minute needles, m. p. 158·5—159·5°, $[\alpha]_D^{20°} \pm 0°$ ($c = 0·41$, in acetone) [Found: C, 57·8; H, 4·79; *M* (Rast), 575. $C_{27}H_{26}O_{13}$ requires C, 58·1; H, 4·69%; *M*, 558].

Gallocatechin (*Substance C*).—Fraction (*c*) (0·5 g.) was dissolved in water at 70° (3 c.c.), and the substance *C* crystallised in minute white needles, decomp. 217—218°, $[\alpha]_D^{22°}$ − 60° (*c* = 0·28, in alcohol) (Found : C, 58·8; H, 4·87%). It yielded an acetate as rhombic plates, m. p. 190·5—192°, $[\alpha]_D^{21°}$ − 14° (*c* = 0·51, in acetone) (Found : C, 58·1; H, 4·83%). These properties agree with the literature values for gallocatechin. For the centrifugal filtration of small quantities of gallocatechin and of the substance *B*, both of which rather readily become brown when exposed to air and light, especially when moist, a form of Skau tube (Fieser, " Experiments in Organic Chemistry," New York, 1941) with a sintered-glass filter disc (No. 2) was found advantageous.

Apparent Partition Coefficients.—It being assumed that in the chromatographic experiments the region of maximum concentration of polyphenol occurs midway in the band, the volume of solvent required to move this region the whole length of the column is $(v_1 + v_2 + v_s)/2 = V_m$, where $v_1 + v_2$ are the volumes of solvent which have passed through the column when the beginning and end respectively of the band are detected in the eluate, and v_s is the volume of the solution. Then *R* as defined by Martin and Synge (*loc. cit.*) is equal to la/V_m, where *l* is the length of the column and *a* is the cross-sectional area of the tube. Hence values for the partition coefficients between water and ether may be calculated by the equation of Martin and Synge. The mean values obtained were 29 for the substance *B* and 56 for gallocatechin. The calculation assumes that no adsorption takes place, a condition which may not be satisfied with silica prepared as described.

Absorption Spectra.—The absorption curve for substance *B* in alcohol (see fig.) showed a maximum at λ max. 271 mμ, with ε max. 1290, and its acetate a similar maximum at λ max. 271 mμ, with ε max. 1430. The spectra of gallocatechin and its acetate in alcohol are almost identical with the above two curves, with λ max. 271 mμ, ε max. 1340 and λ max. 271mμ, ε max. 1260, respectively. In all four curves a shoulder appears at about 280 mμ, but a definite secondary maximum for gallocatechin at this point, reported by Oshima (*loc. cit.*), was not observed. It is noteworthy that, as a fairly good approximation, the absorption maxima both for substance *B* and for gallocatechin can be represented as the sum of the maxima for the chroman (I) and for pyrogallol which have λ max. 272 mμ, ε max. 624 (Morton and Sawires, *J.*, 1940, 1052), and λ max. 266 mμ, ε max. 800 (Goslawski and Marchlewski, *Bull. Acad. Polonaise*, 1931, *A*, 383), respectively.



(I.)

By (Miss) W. B. Wright

Microscopical Examination of Crystals.—(a) *Substance B.* Substance *B* was obtained as prismatic crystals and as fibrous needles, the latter being too small for examination. The former had a mean refractive index of 1·62 and showed inclined and straight extinctions in elongated sections. Maximum extinction angle ~ 18°. *X*-Ray evidence established that the crystals belonged to the monoclinic system, with elongation along the *c* axis. The three principal refractive indices are ~ 1·58 for vibrations parallel to the diad axis, ~ 1·73 for those in a direction 15° from the *c* axis in the acute angle β, and ~ 1·58. For light travelling perpendicular to the *c* axis the crystals have a high double refraction ~ 0·12. Because of the smallness of the crystals an optic picture could not be obtained.

(b) *Acetyl derivative of substance B.* The crystals were fibrous needles of cross section ~ 1 μ. The mean refractive index was with difficulty found to be between 1·54 and 1·58. The fibres exhibited almost straight extinction. No further tests could be applied because of the small crystal size.

(c) *Gallocatechin.* The compound crystallised in bundles of fibrous needles of cross section <1μ. The mean refractive index was determined with great difficulty and found to be *ca.* 1·54. The extinction direction was almost parallel to the length of the fibres. No further information could be obtained because of the small crystal size.

(d) *Gallocatechin hexa-acetate.* The crystals were colourless, foliated, and pinacoidal in form, the pinacoid faces being parallelograms with edge angles of approximately 65° and 115°. The extinction directions were parallel to the bisectors of the angles of the pinacoid faces, and the mean refractive index was 1·56. From *X*-ray evidence it was established that the crystals belonged to the monoclinic system, the pinacoidal faces being (001) faces, and the diad or ortho-axis lying parallel to the bisectors of the obtuse angles of these faces. Owing to the extreme thinness of the crystals (~ 13 μ) only the refractive indices parallel to two of the principal vibration directions could be evaluated, *viz.*, ~ 1·54 for vibrations parallel to the diad axis, and ~ 1·57 for those parallel to the $\bar{a}$ or clino-axis. The crystals possessed a high double refraction ~ 0·20 for light travelling perpendicular to the plane of the plates. An optic picture could not be obtained.

Debye–Scherrer Photographs.—Photographs of powdered samples of the four crystalline materials were taken on a flat plate camera, with a specimen-to-film distance of 5 cm. Copper-*Kα*, nickel-filtered radiation from an *X*-ray tube operated at 30 kv. and 30 ma. was used, and the specimen was rotated during the exposure. The exposure times varied from 5 to 6 hours. The diameters of the diffraction rings so obtained were measured, and the interplanar spacings, in *kX* units, calculated from these, are listed below. Relative intensities, determined visually, are shown in parentheses (V.S. = very strong, S = Strong, F.S. = fairly strong, M = medium, W = weak, V.W. = very weak). Owing to the complexity of the diffraction patterns, these spectra may not be complete.

Compound B.—(*Prismatic form*).

7·37 (F.S.)	6·66 (W.)	6·09 (F.S.)	5·78 (V.W.)	5·35 (F.S.)	5·09 (W.)
4·73 (F.S.)	4·27 (M.)	4·09 (M.)	3·96 (W.)	3·69 (V.S.)	3·43 (V.S.)
3·19 (V.W.)	3·04 (M.)	2·94 (W.)	2·79 (M.)	2·65 (V.W.)	2·61 (V.W.)
2·47 (V.W.)	2·42 (W.)	2·36 (W.)	2·28 (W.)	2·16 (V.W.)	2·11 (V.W.)

(*Needle form*).

5·89 (F.S.)	5·01 (S.)	4·82 (S.)	4·18 (F.S.)	3·72 (V.W.)	3·45 (V.S.)
3·28 (F.S.)	3·12 (F.S.)	2·90 (M.)	2·41 (W.)	2·34 (M.)	

Acetate of compound B.

13·80 (S.)	8·34 (S.)	7·00 (W.)	6·49 (W.)	5·87 (W.)	5·08 (W.)
4·73 (F.S.)	4·27 (S.)	3·94 (W.)	3·78 (W.)	3·61 (W.)	3·49 (F.S.)
3·24 (M.)	3·08 (V.W.)	2·92 (W.)	2·79 (V.W.)	2·70 (V.W.)	2·59 (V.W.)

*Gallocatechin.**

6·25 (F.S.)	5·59 (F.S.)	5·24 (V.W.)	4·85 (S.)	4·45 (F.S.)	4·11 (M.)
3·82 (S.)	3·68 (W.)	3·43 (V.S.)	3·23 (V.W.)	3·11 (F.S.)	2·86 (F.S.)
2·60 (M.)	2·36 (W.)	2·28 (W.)	2·18 (V.W.)	2·09 (M.)	

Gallocatechin hexa-acetate.

11·06 (F.S.)	7·04 (S.)	6·60 (S.)	5·72 (F.S.)	5·32 (V.W.)
4·95 (M.)	4·78½ (M.)	4·36 (V.S.)	4·07 (M.)	3·88 (M.)
3·69 (M.)	3·40 (F.S.)	3·21 (V.W.)	3·08 (V.W.)	2·87 (M.)
2·74 (V.W.)	2·64 (V.W.)	2·51 (V.W.)	2·43 (V.W.)	2·33 (V.W.)

* A different Debye–Scherrer pattern was obtained from one particular specimen of gallocatechin, obtained early in the investigation, presumably a dimorphic form. The pattern given is that observed with all later specimens.

X-Ray Determination of Molecular Weights.—(a) *Substance B.* *X*-Ray measurements were made on a Unicam goniometer with a 6-cm. diameter cylindrical camera, employing copper-$K\alpha$, nickel-filtered radiation (wave length = 1·5387*kX*) from a tube operated at 30 kv. and 15—20 ma. The fibrous crystals of substance *B* (cross section $< 1\ \mu$) were too small for the production of single-crystal oscillation photographs, and as the fibres did not exhibit parallel growth, fibre patterns could not be obtained. The prismatic crystals of substance *B* were extremely small (0·03 × 0·03 × 0·15 mm.), and the cell dimensions and space-group were therefore determined by analysis of a set of oscillation photographs, obtained by oscillating the crystal through 10° angles at 10° intervals about the axis of elongation (the *c* axis). The mean exposure time was in the region of 14 hours. As the high-angle reflections near the fiducial marks were not resolved, an error of 0·5% is allowed in each of the values of $a \sin \beta$, *b*, and *c*, and of 1·5% in the calculated molecular weight. The crystals were examined for the presence of a centre of symmetry by the pyroelectric test. The monoclinic angle was determined by interpretation of reflected spots on the sixth layer lines. The density of the crystals was determined by the flotation method, diluted portions of Thoulet's solution being used. It was best to observe the movements in the liquids of the very small single crystals in polarised light between crossed Nicols. It was found that the prismatic crystals of substance *B* had a monoclinic unit cell with $a \sin \beta = 10{\cdot}73 \pm 0{\cdot}05$ *kX*, $b = 10{\cdot}20 \pm 0{\cdot}05$ *kX*, $c = 12{\cdot}66 \pm 0{\cdot}06$ *kX*, $\beta = 97°\ 30'$. Density = 1·545 ± 0·002 g./c.c. Space-group $P2_1/n$. Number of molecules per unit cell = 4. Hence the molecular weight of substance *B* is calculated to be 324 ± 5.

(b) *Acetyl derivative of substance B.* The fibrous needles of this substance were too small for single-crystal oscillation photographs to be obtained. Crystallised from water–alcohol, the fibres formed bundles with their long axes parallel. From the fibre pattern obtained by oscillating such a bundle about the common axis, the dimensions of the unit cell were found to be approximately 14·8 × 17·1 × 5·5 *kX*. The density of the crystals was 1·37 ± 0·01 g./c.c. The fibres appeared to be weakly pyroelectric. As, also, the crystals show slightly inclined extinction, a monoclinic space-group without a centre of symmetry has been assumed, with two molecules per unit cell. On this assumption, the molecular weight is calculated to be 577 : an accuracy of only about 16% can be claimed for this value.

(c) *Gallocatechin hexa-acetate.* The molecular weight of this substance was determined exactly as for substance *B*, except that, with somewhat larger crystals (0·5 × 0·5 × 0·012 mm.) a shorter exposure time (approx. 2 hours) was required. The lamellar crystals had a monoclinic unit cell with $a \sin \beta = 13{\cdot}12 \pm 0{\cdot}07$ *kX*, $b = 9{\cdot}00 \pm 0{\cdot}05$ *kX*, $c = 11{\cdot}53 \pm 0{\cdot}06$ *kX*, $\beta = 107°$. Density = 1·355 ± 0·002 g./c.c. Space-group $P2_1$. Number of molecules per unit cell = 2. Hence the molecular weight of this hexa-acetate is calculated to be 559 ± 9. The fibrous needles of gallocatechin itself were too small for the production of single-crystal oscillation photographs, and as the fibres did not exhibit parallel growth, fibre patterns could not be obtained.

The work was carried out partly under the auspices of the Research Committee of the Indian Tea Association and partly as an investigation by the Laboratories of J. Lyons & Co. Ltd.

The authors thank Dr. Lampitt for his continued interest in this work.

INDIAN TEA ASSOCIATION.
LYONS LABORATORIES.

[*Received, April 25th,* 1946.]

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8. *The Addition of Thio-compounds to Olefins. Part I. Reactions of Thioglycollic Acid, Thiophenol, and* iso*Pentanethiol.*

By J. I. CUNNEEN.

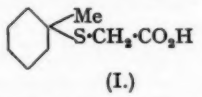
Under peroxidic conditions, *cyclo*hexene and 1-methyl*cyclo*hexene very readily add the fragments formed by scission of the S–H bonds in the thiols named in the title. At the asymmetrically substituted double bond, the orientation of addition is shown to proceed contrary to Markownikoff's rule. Dihydromyrcene and squalene undergo similar but less vigorous reactions, and rubber does not react.

THE interaction of thiols with unsaturated hydrocarbons was first reported by Posner (*Ber.*, **1905**, **38**, 646), who treated thiophenol and benzylthiol with a variety of olefins at room temperature in the presence of acetic and sulphuric acids. With simple olefins, conjugated and non-conjugated, addition of fragments of the thiol produced by scission of the S–H link proceeded readily and, at asymmetrically substituted double bonds, in opposition to Markownikoff's rule: $CR'R''{:}CHR''' + SHPh \longrightarrow CHR'R''{\cdot}CH(SPh)R'''$. More complex non-conjugated olefins (terpinolene and sylvestrene) showed depressed reactivity in that addition occurred at only one double bond, and the highly conjugated systems, stilbene and diphenylbutadiene, failed to react at all. Ashworth and Burkhardt (*J.*, **1928**, 1791) confirmed Posner's formulation of the styrene–thiophenol reaction, and pointed out the catalytic activity of sunlight and the inhibition induced by small amounts of piperidine (cf. also Carothers, *J. Amer. Chem. Soc.*, **1933**, **55**, 2008). Ipatieff and others (*ibid.*, **1938**, **60**, 2731; **1939**, **61**, 71) investigated the reaction of thiophenol and ethanethiol with propylene, *iso*butylene, trimethylethylene, and *iso*propylethylene at 100—150°, and found that, although addition products "abnormal" with respect to Markownikoff's rule were formed in the absence of catalysts, yet the presence of sulphuric acid, contrary to Posner's findings (*loc. cit.*), reversed the orientation of the addition and led to "normal" products. Contemporaneously, Jones and Reid (*J. Amer. Chem. Soc.*, **1938**, **60**, 2452) and Kharasch, Reid, and Mayo (*Chem. and Ind.*, **1938**, **57**, 752) showed that traces of peroxides, either as present normally in unsaturated hydrocarbons or as added ascaridole, strongly catalyse the "abnormal" addition, and that quinol effectively impedes the reaction. Mayo and Walling (*Chem. Reviews*, **1940**, **27**, 387) have proposed a free-radical chain-reaction mechanism, but kinetic evidence on which to found a detailed reaction scheme is so far lacking.

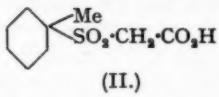
The object of the present work was the preparation of commercially useful rubber derivatives, since this method, with its apparent specificity of double-bond attack and mild reaction conditions, offers a means of introducing various groups along the chain with a high probability of preserving the molecular character of the original polymer. The only other work along these lines is due to Holmberg (*Ber.*, **1932**, **65**, **1349**), whose observations of interaction between thioglycollic acid and rubber, balata, and gutta-percha are, however, of dubious significance (see below). This paper records the reactions of thioglycollic, thiophenol, and *iso*pentanethiol with dihydromyrcene (di-isoprene), squalene (a hexaisoprene), and rubber, and with the simple olefins, *cyclo*hexene and 1-methyl*cyclo*hexene. Experiments with the latter not only permit unequivocal identification of the reaction products by chemical methods, but serve to emphasize an interesting and surprising variation in reactivity among this series of olefins.

Reactions of Thioglycollic Acid.—Although *cyclo*hexene, 1-methyl*cyclo*hexene, and dihydromyrcene are immiscible with the thiol, on shaking equivalent amounts of ordinary laboratory specimens at room temperature a vigorous and highly exothermic reaction occurs immediately. If the olefins were freshly distilled in an atmosphere of nitrogen, reaction was inappreciable, but proceeded almost explosively if a little ascaridole were added. On the other hand, no reaction occurred on mixing squalene with thioglycollic acid containing peroxide, and rubber (which is physically unaffected by the acid) failed to react even under highly favourable peroxidic conditions or irradiation with ultra-violet light.

The first three olefins gave liquid addition products in almost the theoretical yields. From *cyclo*hexene was obtained cyclo*hexylthioglycollic acid*, $C_6H_{11}{\cdot}S{\cdot}CH_2{\cdot}CO_2H$, characterised by oxidation to the crystalline *sulphone*, $C_6H_{11}{\cdot}SO_2{\cdot}CH_2{\cdot}CO_2H$.



(I.)



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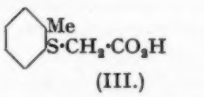
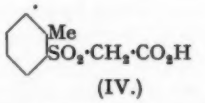


(III.)



(IV.)

1-Methyl*cyclo*hexene gave a corresponding methyl *homologue*, b. p. 135°/0·1 mm., which can either be the "normal" product (I) or the "abnormal" isomer (III), and which yields a crystalline *sulphone*, m. p. 96°, on oxidation (*i.e.*, either II or IV). Reaction of 1-methyl*cyclo*hexanol with thioglycollic acid under acidic conditions produced a *sulphide*, which must be (I), oxidizable to the *sulphone* (II), m. p. 85°, which gave a considerable m. p. depression on admixture with its isomer, m. p. 96°.* The sulphone synthesised *via* the olefin must therefore

* Since the completion of this work, the abstract appeared (*Chem. Abs.*, **1944**, **38**, 3257) of a paper by Hellström and Sandström (*Svensk Kem. Tids.*, **1942**, **54**, 149) not yet available in this country. These authors have also carried out the series of reactions leading to the sulphones (II) and (IV), but whereas (II), for which the m. p. 84—85° is given, is correctly designated, a compound, undoubtedly (IV), having m. p. 92—93°, is described as a sulphonic acid.

be (IV), and its parent sulphide the "abnormal" addition product (II). The "normal" sulphide was also obtained by reaction of the olefin and thioglycollic acid in 75% sulphuric acid at 0°, thus supporting Ipatieff's conclusions already mentioned concerning the directive influence of an acidic environment. Dihydromyrcene yielded two liquid *sulphides* corresponding to

$$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CHMe{\cdot}S{\cdot}CH_2{\cdot}CO_2H \quad (V.)$$
$$CHMe_2{\cdot}CH(S{\cdot}CH_2{\cdot}CO_2H){\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CHMe{\cdot}S{\cdot}CH_2{\cdot}CO_2H \quad (VI.)$$

the mono- * or di-addition compounds (V) and (VI). The *sulphone* derived from (VI) was analytically pure but failed to crystallise.

Reactions of Thiophenol.—Both *cyclo*hexenes and dihydromyrcene, squalene, and rubber dissolve in thiophenol without noticeable evolution of heat. Irradiation of the solution at room temperature with a quartz mercury-vapour lamp for a few hours initiated reaction with the first four olefins and produced high yields of sulphides, but again rubber was almost completely resistant. *cyclo*Hexene gave the liquid *sulphide*, $C_6H_{11}{\cdot}SPh$, characterised by the crystalline *sulphone*, $C_6H_{11}{\cdot}SO_2Ph$. 1-Methyl*cyclo*hexene gave the *sulphide* (VII) whose constitution was established by the non-identity of its derived *sulphone* with that synthesised from

(VII.)

(VIII.)

the authentically "normal" *sulphide* (VIII). Ultra-violet absorption also served as a specific criterion for distinguishing the sulphides. The spectrum of (VII), resembling that of *cyclo*hexyl phenyl sulphide, has an intense band with a maximum at 2585 A. ($\epsilon = 7000$) arising from conjugation of the sulphur atom with the adjacent phenyl group. Models show that in (VIII) steric hindrance by the methyl group interferes with the co-planarity of the sulphur valencies and the benzene ring which is essential to full development of such conjugation and, in agreement with this, the associated band is practically absent from the spectrum of (VIII). Analogously to its reaction with the thioglycollic acid, dihydromyrcene yielded a mixture of *mono-* and *di-adducts*. The pale yellow viscous reaction product from squalene was freed from excess of thiol by heating to 100° on a high-vacuum line, and analysis then showed moderate incorporation of thiophenol, but no attempt was made to separate and purify the mixture of phenyl squalene sulphides.†

Reactions of iso*Pentanethiol.*—Irradiation with ultra-violet light of a mixture of *cyclo*hexene and the thiol yields the *sulphide* $C_6H_{11}{\cdot}SC_5H_{11}$, which can be oxidised to the *sulphone* $C_6H_{11}{\cdot}SO_2{\cdot}C_5H_{11}$. The corresponding *sulphide* from 1-methyl*cyclo*hexene was obtained by heating a mixture of the reagents to 100° for 12 hours, but since the derived sulphone failed to crystallise, it is not possible to prove whether "normal" or "abnormal" addition occurs. A mixture of dihydromyrcene and the thiol, left in daylight at room temperature for a year, gave a mixture of mono- and di-adducts. Squalene behaved as described for *cyclo*hexene, but again rubber remained inert.

Discussion.—The general characteristics of the reactions described above are typical of the peroxide-catalysed additions so extensively explored by Kharasch and his school (for complete list of references, see Mayo and Walling, *loc. cit.*). The most notable feature is the inexplicable reluctance of rubber to react with either of the thiols—the case of thiophenol, an excellent solvent for rubber, effectively disproving any suggestion that insufficient contact of the reactants is responsible, as indeed might be argued with thioglycollic acid. Holmberg's (*loc. cit.*) claim to have obtained reaction with the latter compound by immersing rubber strips for up to two years at room temperature is open to question. According to him, the rubber, completely insoluble at the start, gradually swells and eventually dissolves, forming a homogeneous solution. The author's experience is that small pieces of rubber in excess of the thiol, with or without ascaridole, sealed up in a vacuum and left for two years, are inappreciably swollen, much less dissolved. Holmberg's mixtures presumably had access to air, however, and catalytic activity by oxygen may have promoted the reported addition. On the other hand, thioglycollic acid itself is readily oxidised on atmospheric exposure (Klason, *Ber.*, 1881, **14**, 410) so that reactions secondary to this may have initiated the observed changes. The

* No attempt is made to distinguish between the two different isomers which result from additions at either of the double bonds, and in this and the following paper the formulæ for the *mono*-adducts are arbitrary in this respect.

† To avoid other ambiguity and for general simplicity, the polyisoprene adducts are designated throughout this and the following paper as, *e.g.*, phenyl squalene sulphide, it being understood that a hydrogen atom is added together with the thio-radical to give the respective sulphur derivative of a saturated hydrocarbon as shown in the various formulæ.

inertness of rubber seems to represent the extreme of a reactivity trend, *cyclo*hexene > dihydromyrcene > squalene > rubber, of as yet unknown origin.

As regards the activity of the addenda, the order appears qualitatively as, thioglycollic acid > thiophenol ~ *iso*pentanethiol, which parallels the strength of the related carboxylic acids, malonic, benzoic, and *iso*valeric. This suggests that the ease of active hydrogen atom and proton removal are similarly conditioned, and that the rupture of the S–H link provides the main contribution to the activation energy and heat of reaction of the addition process.

Experimental

Reactions with Thioglycollic Acid.—(A) *cyclo*Hexene (8·2 g.) was shaken with thioglycollic acid (9·2 g.) for 15 mins., a homogeneous solution resulting. After removal of traces of unchanged reactants at 100° in a vacuum, distillation yielded cyclo*hexylthioglycollic acid* (14·5 g.), b. p. 122°/0·1 mm. (Found: C, 55·3; H, 8·1; S, 18·1; equiv., 176. $C_8H_{14}O_2S$ requires C, 55·2; H, 8·05; S, 18·4%; equiv., 174).

To the above acid (5 g.) in chloroform (60 c.c.) were added ice, 3N-sulphuric acid (170 c.c.), and then powdered potassium permanganate (8 g.) in small portions with constant shaking. The mixture was then allowed to attain room temperature, decolourised with aqueous sodium bisulphite, the chloroform layer separated, and the aqueous layer extracted with more chloroform. The combined extracts were dried (Na_2SO_4) and concentrated to give the crude solid *sulphone*, which crystallised from benzene in glistening needles, m. p. 82° (Found: C, 46·4; H, 6·8; S, 15·25; equiv., 200. $C_8H_{14}O_4S$ requires C, 46·6; H, 6·8; S, 15·5%; equiv., 206).

(B) 1-*Methyl*cyclo*hexene*. The olefin (9·6 g.) reacted vigorously with the thio-acid (9·2 g.), the product, isolated by distillation, being 2-*methyl*cyclo*hexylthioglycollic acid* (III), b. p. 135°/0·1 mm. (Found: C, 56·9; H, 8·6; S, 16·6; equiv., 191. $C_9H_{16}O_2S$ requires C, 57·4; H, 8·4; S, 17·0%; equiv., 188).

Oxidation of this sulphide (5 g.) exactly as described for the *cyclo*hexyl homologue gave 4·5 g. of the crude *sulphone* (IV), which separated from benzene–light petroleum (b. p. 100—120°) as colourless plates, m. p. 96° (Found: C, 48·7; H, 7·3; S, 14·15; equiv., 216. $C_9H_{16}O_4S$ requires C, 49·1; H, 7·3; S, 14·55%; equiv., 220).

Preparation of 1-*methyl*cyclo*hexylthioglycollic acid* (I). (i) 1-Methyl*cyclo*hexanol (21 g.) was heated with thioglycollic acid (24 g.) and 2N-hydrochloric acid (220 c.c.) for 4 hours at 110°. The cooled mixture was extracted three times with chloroform, the extracts dried (Na_2SO_4), then concentrated to yield a yellow oil (15 g.), which was dissolved in 2N-potassium hydroxide, and any unchanged methyl-*cyclo*hexanol removed by ether extraction. Distillation of the purified oil, regenerated from the alkaline solution by acidification, gave 1-*methyl*cyclo*hexylthioglycollic acid*, b. p. 147°/0·1 mm. (Found: C, 57·5; H, 8·4; S, 16·5%; equiv., 189). (ii) Thioglycollic acid (4·6 g.) was slowly added to a rapidly stirred solution of 1-methyl*cyclo*hexene (9·6 g.) in 75% aqueous sulphuric acid (50 g.) cooled to 0°. When addition was complete, the mixture was allowed to warm to room temperature, and stirring continued for a further 15 mins. The product isolated by ether extraction was purified *via* an aqueous alkaline solution as under (i) and then distilled; b. p. 142°/0·1 mm. (Found: C, 57·3; H, 8·6; S, 16·7%; equiv., 193).

The *sulphone* (II) of the acid (I), prepared in the usual manner and recrystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 85° (Found: C, 49·9; H, 7·4; S, 14·2%; equiv., 218). A mixed m. p. with the 2-methyl isomer (IV) showed a depression of 20—25°.

(C) *Dihydromyrcene*. (*a*) The olefin (10 g.) (Found: C, 87·05; H, 13·0%; I.V., 364. Calc. for $C_{10}H_{18}|=_2$: C, 86·9; H, 13·1%; I.V., 368) was shaken for 30 mins. with the quantity (6·5 g.) of thio-acid required to saturate one double bond; the resulting homogeneous solution was diluted with benzene (200 c.c.), and unchanged thioglycollic acid removed by several washings with water. Fractionation of the oil obtained from the benzene solution gave: (i) dihydromyrcene, b. p. <140°/14 mm. (1·2 g.); (ii) *dihydromyrcene monothioglycollic acid* (V), b. p. 170°/0·1 mm. (7·9 g.) (Found: C, 62·55; H, 9·6; S, 13·8; equiv., 234. $C_{12}H_{22}O_2S$ requires C, 62·6; H, 9·6; S, 13·9%; equiv., 230); (iii) high-boiling residue of uncertain composition (5·4 g.). (*b*) The reaction was repeated but with excess of thio-glycollic acid, the product being taken up in benzene and freed from unchanged acid as before. Concentration of the benzene solution gave a viscous oil which, after being kept at 100° in a high vacuum to remove any hydrocarbon, analysed correctly for *dihydromyrcene bis(thioglycollic acid)* (VI) (Found: C, 52·15; H, 8·0; S, 19·65. $C_{14}H_{26}O_4S_2$ requires C, 52·25; H, 8·1; S, 19·8%).

Oxidation of the latter acid (VI), carried out in the usual way, yielded a viscous gum which failed to crystallise although analysis showed it to be the desired *sulphone* (Found: C, 43·2; H, 6·8; S, 16·0. $C_{14}H_{26}O_8S_2$ requires C, 43·5; H, 6·7; S, 16·6%).

(D) *Squalene*. The hydrocarbon (1 g.) was shaken with the acid (3 g.) and a little ascaridole (0·05 g.) for several weeks at room temperature. The mixture, which remained heterogeneous, was worked up as described for the dihydromyrcene products but gave only unchanged squalene.

(E) *Rubber*. (i) Sol rubber (1 g.) was dissolved in benzene (20 c.c.) containing thioglycollic acid (2 g.) and ascaridole (0·05 g.), and the solution sealed under a vacuum in a "Pyrex" tube 1·5 cm. in diameter. The tube was irradiated for 20 hrs. by a Hanovia S. 500 mercury-vapour lamp placed 6 in. distant. The product, obtained by precipitation with ethyl alcohol followed by extraction (Soxhlet) with alcohol in an atmosphere of nitrogen for 24 hrs., was a white rubber superficially indistinguishable from the starting material (Found: S, 1·7%, which corresponds to 3·8% addition). (ii) A similar reaction mixture to that in (i) was sealed in a vacuum and kept in the laboratory for 2 years; a virtually unchanged rubber resulted (Found: S, 1·1%, *i.e.*, 2·4% addition). (iii) The rubber (1 g.), cut into small pieces, was suspended in thioglycollic acid (10 g.) containing ascaridole (0·05 g.), and the mixture sealed off under a vacuum, and left for 2 years. At the end of this time, the rubber nodules, which showed no sign of change, were removed and well washed with alcohol (Found: S, 0·75%).

Reactions with Thiophenol.—(A) cyclo*Hexene*. The olefin (8·2 g.) was dissolved in thiophenol (11

g.), and the solution irradiated with the mercury lamp for 8 hrs. The product, freed from unchanged reactants, was a yellow oil (16 g.) which consisted almost entirely of cyclo*hexyl phenyl sulphide*, b. p. 108°/0·1 mm. (Found: C, 74·95; H, 8·35; S, 16·6. $C_{12}H_{16}S$ requires C, 75·0; H, 8·3; S, 16·65%). Light absorption in *cyclo*hexane showed $\lambda_{max.}$ 2575 A. ($\epsilon = 5800$).

Oxidation of the sulphide in the usual way gave the *sulphone*, which crystallised from methyl alcohol in colourless cubes, m. p. 74° (Found: C, 64·1; H, 7·2; S, 14·1. $C_{12}H_{16}O_2S$ requires C, 64·25; H, 7·1; S, 14·3%).

(B) 1-*Methyl*cyclo*hexene*. Prepared from the hydrocarbon (9·6 g.) and the thiol (11 g.) just as was the *cyclo*hexene derivative, 2-*methyl*cyclo*hexyl phenyl sulphide* (VII) had b. p. 120°/0·1 mm. (Found: C, 75·6; H, 8·75; S, 15·35. $C_{13}H_{18}S$ requires C, 75·6; H, 8·75; S, 15·55%); $\lambda_{max.}$ 2585 A. ($\epsilon = 7000$) in *cyclo*hexane.

The *sulphone* crystallised from methyl alcohol in needles, m. p. 108° (Found: C, 65·5; H, 7·6; S, 13·25. $C_{13}H_{18}O_2S$ requires C, 65·5; H, 7·6; S, 13·45%).

Preparation of 1-*methyl*cyclo*hexyl phenyl sulphide* (VIII). 1-Methyl*cyclo*hexene (9·6 g.) was treated with thiophenol (5·5 g.) in the presence of 75% aqueous sulphuric acid (50 g.) as described for the preparation of 1-methyl*cyclo*hexylthioglycollic acid, method (ii). The required *sulphide* was obtained as an oil, b. p. 123°/0·1 mm. (Found: C, 75·6; H, 8·8; S, 15·25%), with $\lambda_{max.}$ 2680 A. ($\epsilon = 1500$) in *cyclo*hexane. The corresponding *sulphone* crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 76° (Found: C, 65·5; H, 7·6; S, 13·3%). A mixed m. p. with the 2-methyl isomer showed a depression of 20—30°.

(C) *Dihydromyrcene*. Irradiation of a solution of the hydrocarbon (7 g.) in the thiol (10 g.) with the mercury lamp for 8 hrs. yielded an oil (12·2 g.) separable by fractional distillation into *phenyl dihydromyrcene sulphide* (8 g.), b. p. 135°/0·05 mm. (Found: C, 77·2; H, 9·65; S, 13·1. $C_{16}H_{24}S$ requires C, 77·4; H, 9·7; S, 12·9%), and *dihydromyrcene bis(phenyl sulphide)* (3·4 g.), a viscous syrup, b. p. 185°/0·05 mm. (Found: C, 73·5; H, 8·25; S, 17·85. $C_{22}H_{30}S_2$ requires C, 73·8; H, 8·4; S, 17·85%).

(D) *Squalene*. The hydrocarbon (1 g.), thiophenol (2 g.), and ascaridole (0·05 g.) were sealed in a vacuum and irradiated with ultra-violet light for 8 hrs. Removal of unchanged reactants by heating to 100° at 10^{-5} mm. left a mixture evidently consisting of phenyl squalene sulphides (Found: C, 76·6; H, 8·95; S, 13·8. Calc. for 56% addition: C, 77·4; H, 9·0; S, 13·8%).

(E) *Rubber*. (i) A solution of sol rubber (1 g.), the thiol (2 g.), benzene (20 c.c.), and ascaridole (0·05 g.) was sealed under vacuum in a "Pyrex" tube and irradiated as before for 16 hrs. The product, practically unchanged rubber, had S, 1·45% (*i.e.*, corresponding to 3·25% addition). (ii) A solution of rubber in the thiol (10 g.) without benzene was now employed, and the reaction conditions of (i) repeated. The product had S, 1·8%. (iii) A similar solution to that used in (ii) was sealed in a vacuum and left at room temperature for 2 years. Again, the rubber had undergone little change (Found: S, 1·15%).

Reactions with iso*Pentanethiol*.—(A) cyclo*Hexene*. A solution of the olefin (8 g.) in the thiol (8 g.) was irradiated for 8 hrs., the product freed from the starting materials by heating to 100° at 25 mm. pressure, and the residual oil (12 g.) distilled. The exclusive product was cyclo*hexyl* iso*amyl sulphide*, b. p. 120°/12 mm. (Found: C, 70·9; H, 11·85; S, 17·5. $C_{11}H_{22}S$ requires C, 71·0; H, 11·8; S, 17·2%). The usual oxidation procedure gave the *sulphone* as an oil which crystallised with some difficulty from ice-cold light petroleum (b. p. 40—60°) as flat leaflets, m. p. 54—56° (Found: C, 59·5; H, 10·0; S, 14·7. $C_{11}H_{22}O_2S$ requires C, 60·5; H, 10·1; S, 14·6%).

(B) 1-*Methyl*cyclo*hexene*. The olefin (10 g.) and thiol (10 g.) were refluxed together for 12 hrs. When freed from excess of reactants, the sole product was a *methyl*cyclo*hexyl* iso*amyl sulphide*, b. p. 124°/10 mm., which is probably the 2-methyl isomer although this was not formally proved (Found: S, 16·1. $C_{12}H_{24}S$ requires S, 16·0%). By the normal procedure, the *sulphone* was obtained as an oil, b. p. 149°/0·1 mm. (Found: C, 61·6; H, 10·3; S, 13·5. $C_{12}H_{24}O_2S$ requires C, 62·1; H, 10·35; S, 13·8%).

(C) *Dihydromyrcene*. The hydrocarbon (10 g.) was dissolved in the thiol (16 g.), and the solution sealed in a vacuum, and left in the laboratory for a year. Fractionation of the product gave: (i) unchanged reactants contaminated with a little sulphide, b. p. <148°/10 mm. (6·2 g.); (ii) iso*amyl dihydromyrcene sulphide* (Found: C, 73·7; H, 12·3; S, 13·8. $C_{15}H_{30}S$ requires C, 74·4; H, 12·4; S, 13·2%), b. p. 158/10 mm. (6·3 g.); (iii) material of b. p. <170°/0·05 mm. consisting of a mixture of (ii) and (iv); and (iv) *dihydromyrcene bis*(iso*amyl sulphide*) (Found: C, 69·35; H, 12·05; S, 17·9. $C_{30}H_{62}S_2$ requires C, 69·4; H, 12·8; S, 18·5%), b. p. 171—174°/0·05 mm. (12·0 g.).

(D) *Squalene*. Squalene (1 g.), the thiol (2 g.), and ascaridole (0·05 g.) were sealed together in a vacuum and irradiated for 16 hrs. with the mercury-vapour lamp. The product, freed from unchanged reactants, was a viscous oil (1·8 g.) (Found: S, 16·5. Calc. for 76% addition: S, 16·5%).

(E) *Rubber*. (i) Sol rubber (1 g.), dissolved in benzene (20 c.c.) containing the thiol (2 g.) and ascaridole (0·1 g.), was sealed in a "Pyrex" tube under a vacuum and irradiated as before for 16 hrs. The solution had then set to a stiff gel, but on trituration with alcohol and drying in a vacuum an insignificantly changed rubber of low sulphur content was obtained (0·9 g.) (Found: S, 0·95%). (ii) A similar solution to that used in (i) was sealed in a vacuum and kept at room temperature for 2 years. Isolated by alcohol precipitation, the rubber was practically unchanged (Found: S, 0·7%).

I thank Dr. W. T. Chambers and Miss H. Rhodes for carrying out the microanalyses, and Dr. H. P. Koch for the spectrographic measurements in this work, which forms part of the programme of fundamental research on rubber undertaken by the Board of the British Rubber Producers' Research Association.

BRITISH RUBBER PRODUCERS' RESEARCH ASSOCIATION,
48 TEWIN ROAD, WELWYN GARDEN CITY.

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9. *Synthetic Antimalarials. Part XI. The Effect of Variation of Substituents in Derivatives of Mono- and Di-alkylpyrimidines.*

By R. Hull, (Miss) B. J. Lovell, H. T. Openshaw, and A. R. Todd.

Following the discovery that certain 2-amino-4-dialkylaminoalkylamino-5 : 6-dialkylpyrimidines have marked antimalarial activity (Hull, Lovell, Openshaw, Payman, and Todd, Part III, *J.*, 1946, 357) a more extended investigation has been made of the effects of variation of substituents in compounds of this type. In addition several other series of simple mono- and di-methylpyrimidine derivatives bearing amino- and dialkylaminoalkylamino-substitutents have been synthesised; a number of the individual substances have been found to be active against *P. gallinaceum* in chicks.

In Part III (*loc. cit.*) the preparation of a number of derivatives of mono- and di-alkylpyrimidines containing as additional substituents an amino- and a dialkylaminoalkylamino-group was described. The discovery that marked antimalarial activity was possessed by substituted 5 : 6-dimethylpyrimidines of type (I) encouraged us to extend our study of such simple pyrimidine derivatives in the hope both of finding therapeutically useful compounds, and of discovering some connection between antimalarial activity and the chemical structure of the substances. In particular, we wished, if possible, to obtain further evidence bearing on the hypothesis advanced in Part III that interference with an adenosine-containing enzyme system might be responsible for the biological activity of this group of substances. The effect of some variations in the nature of the basic side chain (R″) and of the alkyl groups (R, R′) in pyrimidines of type (I) has already been described. In the present paper we describe some further modifications of the type structure (I), and also several other series of pyrimidine derivatives having different orientations of amino-, alkyl, and dialkylaminoalkylamino-substituents.

It has already been shown that a 5-alkyl group is necessary to promote activity in compounds of type (I). The presence of a 6-substituent in (I), however, is not essential; thus 2-amino-4-β-diethylaminoethylamino-5-methylpyrimidine (I; R = H, R′ = Me, R″ = $[CH_2]_2{\cdot}NEt_2$) and *2-amino-4-γ-diethylaminopropylamino-5-methylpyrimidine* (I; R = H, R′ = Me, R″ = $[CH_2]_3{\cdot}NEt_2$) were both highly active against *P. gallinaceum* in chicks at a dose of 80 mg./kg. Substitution of a phenoxy-group for the methyl group in these compounds (I; R = H, R′ = OPh, R″ = $[CH_2]_2{\cdot}NEt_2$ or $[CH_2]_3{\cdot}NEt_2$) reduced, but did not entirely destroy, the activity. A bromo-substituent at the 5-position was not capable of conferring activity; the 5-bromo-2-amino-4-dialkylaminoalkylamino-6-methylpyrimidines (I; R = Me, R′ = Br, R″ = $[CH_2]_2{\cdot}NEt_2$ or $[CH_2]_3{\cdot}NEt_2$) were inactive at a dose of 120 mg./kg. Other variations of type (I) included the replacement of the 6-methyl group by an amino-group, a chlorine atom, or a second diethylaminoethyl group. The antimalarial activity of the compounds is given in Table I.

The compounds mentioned above were prepared from the corresponding substituted 4-chloropyrimidines by the general method described in Part III (*loc. cit.*). *4-Chloro-2-amino-5-methylpyrimidine* was obtained by the interaction of phosphoryl chloride and 2-amino-4-hydroxy-5-methylpyrimidine (Johnson and Clapp, *Amer. Chem. J.*, 1904, **32**, 130). The similar replacement by chlorine of the hydroxy-group of *2-amino-4-hydroxy-5-phenoxypyrimidine* gave unsatisfactory results, and to overcome this difficulty the substance was acetylated. Instead of the expected 2-acetamido-compound, a *substance*, $C_{24}H_{20}O_5N_6$, was obtained; treatment of this with phosphoryl chloride, however, gave *4-chloro-2-acetamido-5-phenoxypyrimidine*. After condensation with the appropriate diamine, the acetyl group was removed by hydrolysis. When treated with an excess of β-diethylaminoethylamine in the usual manner, *4-chloro-5-bromo-2-amino-6-methylpyrimidine* suffers partial replacement of the bromine atom, but by interaction with an equimolecular quantity of the amine the chlorine atom alone is replaced. The 2 : 6-diamino-4-dialkylaminoalkylaminopyrimidines (I; R = NH_2, R′ = H) were obtained by the interaction of equimolecular quantities of 4-chloro-2 : 6-diaminopyrimidine (Büttner, *Ber.*, 1903, **36**, 2227) and the appropriate diamine; when excess of diamine was used 2-amino-4 : 6-bis(dialkylaminoalkylamino)pyrimidines were obtained, the structure of the products being proved by an independent preparation of one of them from 4-chloro-2-amino-6-β-diethylaminoethylaminopyrimidine (Curd *et al.*, forthcoming publication) and β-diethylaminoethylamine.

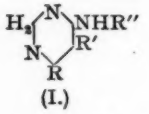
Of the six possible isomerides (II—VII) of the type structure (I), representatives of five (II—VI) are described in this paper; in addition, some monomethylpyrimidines (types VIII and IX) allied to (II) and (III) have been studied. The results of biological tests against *P.*

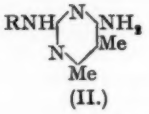
TABLE I.

Antimalarial Activity of Derivatives of 2-Aminopyrimidine (Type I).

Substituents at positions. 4.	5.	6.	Dose (mg./kg.).	Activity.
$NH\cdot[CH_2]_2\cdot NEt_2$	Me	H	160	++
			80	++
			40	−
$NH\cdot[CH_2]_3\cdot NEt_2$	Me	H	160	Toxic
			80	++
			40	+
$NH\cdot[CH_2]_2\cdot NEt_2$	OPh	H	120	+
			60	±
$NH\cdot[CH_2]_3\cdot NEt_2$	OPh	H	240	Toxic
			120	±
			40	−
$NH\cdot[CH_2]_2\cdot NEt_2$	Br	Me	120	−
			80	−
$NH\cdot[CH_2]_3\cdot NEt_2$	Br	Me	120	−
			80	−
$NH\cdot[CH_2]_2\cdot NEt_2$	H	NH_2	240	−
$NH\cdot[CH_2]_3\cdot NEt_2$	H	NH_2	240	Toxic
			120	−
$NH\cdot[CH_2]_2\cdot NEt_2$	H	$NH\cdot[CH_2]_2\cdot NEt_2$	160	±
			40	−
$NH\cdot[CH_2]_2\cdot NEt_2$	Me	NH_2	80	Toxic
			40	−
$NH\cdot[CH_2]_3\cdot NEt_2$	Me	NH_2	80	Toxic
			40	−
$NH\cdot[CH_2]_2\cdot NEt_2$	Me	Cl	160	Toxic
			80	−
$NH\cdot[CH_2]_3\cdot NEt_2$	Me	Cl	160	Toxic
			40	Toxic
			20	−

gallinaceum in chicks carried out with these substances are shown in Table II. It will be seen that only among compounds of type (III) was marked activity observed; one of them,


(I.)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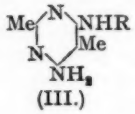
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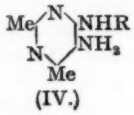
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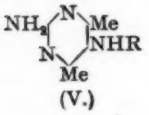
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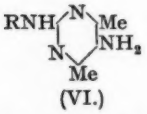
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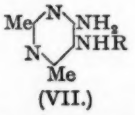
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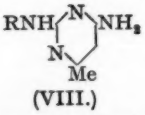
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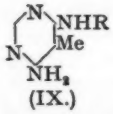

(IX.)

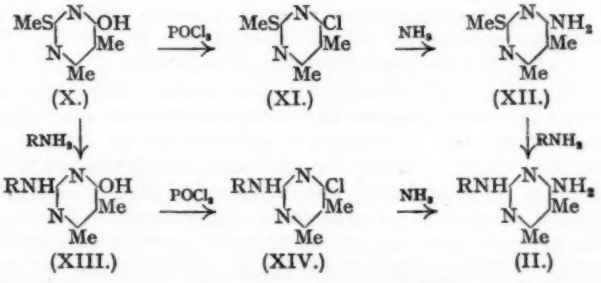
4-amino-6-γ-diethylaminopropylamino-2 : 5-dimethylpyrimidine (III; R = $[CH_2]_3\cdot NEt_2$) is the most active of all the simple pyrimidines we have prepared, appreciable activity being observed at a dose of 20 mg./kg. It is difficult to make any generalisations about structure and antimalarial activity on the basis of results so far obtained but it is interesting that the most active compounds we have prepared have structures which are compatible with the hypothetical mode of action tentatively advanced by us in Part III (*loc. cit.*). It is clearly impossible to argue the validity of any concept of action based on interference with the synthesis or functioning of enzyme components in the absence of extensive biological investigations, but there would seem to be some justification for its retention at present as a basis for further work. The weak activity shown by (V; R = $[CH_2]_3\cdot NEt_2$) is of some interest in connection with the views on the relation between structure and plasmodial action originally advanced by Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) and recently modified by Curd and Rose (Part X; *J.*, 1946, 729). It is difficult to formulate any *o*- or *p*-quinonoid tautomer of (V) involving the basic side chain.

The starting point for the synthesis of compounds of type (II) was 4-hydroxy-2-methylthio-5 : 6-dimethylpyrimidine (X), readily obtained by the interaction of ethyl α-methylacetoacetate with *S*-methyl*iso*thiourea; the substance had previously been prepared (Chi and Kao, *J. Amer. Chem. Soc.*, 1936, **58**, 769) by methylation of the 2-thiol compound. In the first route investigated (X) was converted through *4-chloro-2-methylthio-5 : 6-dimethylpyrimidine* (XI) into

TABLE II.

Type.	R.	Dose (mg./kg.).	Activity.
III	$[CH_2]_2 \cdot NEt_2$	80	++
		40	++
III	$[CH_2]_3 \cdot NEt_2$	80	++
		40	++
		20	+
III	$[CH_2]_3 \cdot NMe_2$	160	++
		80	+
II	$[CH_2]_2 \cdot NEt_2$	160	−
II	$[CH_2]_3 \cdot NEt_2$	80	±
		40	−
II	$[CH_2]_3 \cdot NBu^{\alpha}_2$	80	Toxic
		40	−
VIII	$[CH_2]_2 \cdot NEt_2$	160	Toxic
		80	−
VIII	$[CH_2]_3 \cdot NEt_2$	160	Toxic
		80	−
VIII	$[CH_2]_3 \cdot NBu^{\alpha}_2$	80	Toxic
		40	+
		20	−
VIII	$[CH_2]_3 \cdot NMe_2$	160	±
		80	−
IV	$[CH_2]_2 \cdot NEt_2$	160	−
IV	$[CH_2]_3 \cdot NEt_2$	160	−
IV	$[CH_2]_3 \cdot NBu^{\alpha}_2$	80	Toxic
V	$[CH_2]_3 \cdot NEt_2$	160	+
		80	−
IX	$[CH_2]_3 \cdot NEt_2$	120	−
IX	$[CH_2]_3 \cdot NEt_2$	160	Toxic
		80	−

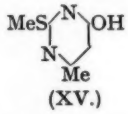
4-amino-2-methylthio-5 : 6-dimethylpyrimidine (XII); the second step was accompanied by some loss of methylthiol with formation of 2 : 4-diamino-5 : 6-dimethylpyrimidine. The substance (XII) when heated with γ-diethylaminopropylamine gave the desired *product* (II; $R = [CH_2]_3 \cdot NEt_2$). Analogous reactions with other dialkylaminoalkylamines proved unsatisfactory, however, and an alternative route was therefore employed. The substance (X) reacted smoothly with amines to form 2-dialkylaminoalkylamino-4-hydroxy-5 : 6-dimethylpyrimidines (XIII), which were converted through the chloro-compounds (XIV) into the desired products (II).



With one exception, the corresponding derivatives (VIII) of 6-methylpyrimidine were prepared from 4-hydroxy-2-methylthio-6-methylpyrimidine by the second route mentioned in the preceding paragraph; the intermediate chloro-compounds have been described in Part VI of this series (Curd, Davis, Owen, Rose, and Tuey, *J.*, 1946, 370). In the case where $R = [CH_2]_3 \cdot NMe_2$ the yields obtained by this method proved to be unsatisfactory and the first method was successfully employed. *4-Amino-2-methylthio-6-methylpyrimidine* (XVI) was readily obtained by amination of the 4-chloro-compound (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 435), and on heating with dimethylaminopropylamine it gave an almost theoretical yield of the desired product (VIII; $R = [CH_2]_3NMe_2$).

Variation in the reactivity of 2-methylthiopyrimidines towards amines has been noted previously; thus Curd and Rose (Part I, *J.*, 1946, 343) found that 2-methylthio-4 : 6-dimethylpyrimidine reacted only sluggishly with aniline at a high temperature, whereas 4-hydroxy-2-methylthio-6-methylpyrimidine (XV) reacted readily and completely at a much lower temperature and they attributed this difference in behaviour to the tautomeric character

of (XV). It is clear from the fact that (XVI) is less reactive than (XV) in this sense that this view requires some expansion, but available data are insufficient to permit a wholly satisfactory explanation on theoretical grounds.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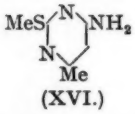
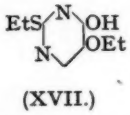
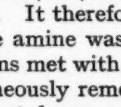

(XVI.)

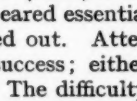

(XVII.)

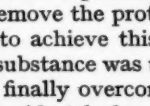
It appears from the present work that the reactivity of the 2-methylthio-group is also adversely affected by a methyl group at C_5. A similar effect was noted by Johnson and Heyl (*Amer. Chem. J.*, 1907, **38**, 237) who found that, whereas 4-hydroxy-2-ethylthiopyrimidine reacted readily with aniline at 100°, the 5-ethoxy-derivative (XVII) reacted only slowly at 200°. An *o–p*-directive group at C_5 will tend to increase the electron-availability at the *p*-position (C_2) and thus diminish the ease of attack by an amine.

Substances of type (III) were prepared in the usual manner from 4-chloro-6-amino-2 : 5-dimethylpyrimidine (Huber and Hölscher, *Ber.*, 1938, **71**, 92) and the appropriate amines. The related derivatives (IX) of 5-methylpyrimidine were prepared by a similar series of reactions. 4 : 6-*Dihydroxy*-5-*methylpyrimidine*, obtained by the condensation of formamidine with ethyl methylmalonate, was converted through 4 : 6-*dichloro*-5-*methylpyrimidine* into 4-*chloro*-6-*amino*-5-*methylpyrimidine* which was treated with dialkylaminoalkylamines in the usual manner.

5-Amino-2 : 6-dimethylpyrimidines carrying a basic side chain at C_4 (type IV) were prepared by interaction of the appropriate amines and 4-chloro-5-amino-2 : 6-dimethylpyrimidine (XIX; R = H). 5-Amino-4-hydroxy-2 : 6-dimethylpyrimidine (XVIII; R = NH_2) was conveniently obtained by hydrogenation of 5-benzeneazo-4-hydroxy-2 : 6-dimethylpyrimidine (XVIII; R = PhN_2) (Andersag and Westphal, *Ber.*, 1937, **70**, 2035) using a palladised barium sulphate catalyst, but the direct conversion of the former into 4-chloro-5-amino-2 : 6-dimethylpyrimidine (XIX; R = H) by means of phosphoryl chloride (cf. Andersag and Westphal, *loc. cit.*) gave, in our experience, only a very poor yield. Since it seemed probable that this was due to the reactivity of the 5-amino-group, the effect of protecting this group prior to chlorination was investigated. Attempts to replace the hydroxyl group of the benzeneazo-compound (XVIII; R = PhN_2) by chlorine were unsuccessful. The chlorination of 5-*acetamido*-4-*hydroxy*-2 : 6-*dimethylpyrimidine* (XVIII; R = NHAc), however, proceeded readily with phosphoryl chloride and dimethylaniline (Baddiley and Topham, *J.*, 1944, 678); the resulting 4-*chloro*-5-*acetamido*-2 : 6-*dimethylpyrimidine* (XIX; R = Ac) reacted readily with γ-diethylaminopropylamine, but on attempting to remove the acetyl group by hydrolysis the product (XX; R = $[CH_2]_3{\cdot}NEt_2$) cyclised to 9-γ-*diethylaminopropyl*-2 : 6 : 8-*trimethylpurine* (XXI; R = $[CH_2]_3{\cdot}NEt_2$). Treatment of (XIX; R = Ac) with other dialkylaminoalkylamines gave a mixture of the corresponding pyrimidine (XX) and purine (XXI) derivatives. The purines (XXI) were devoid of antimalarial activity. It therefore appeared essential to remove the protecting acetyl group before reaction with the amine was carried out. Attempts to achieve this by hydrolysis under a variety of conditions met with little success; either the substance was unaffected or the chlorine atom was simultaneously removed. The difficulty was finally overcome by employing a formyl in place of an acetyl group for protection. 5-*Formamido*-4-*hydroxy*-2 : 6-*dimethylpyrimidine* (XVIII; R = NH·CHO) was treated with phosphoryl chloride and dimethylaniline and the resulting 4-*chloro*-5-*formamido*-2 : 6-*dimethylpyrimidine* (XIX; R = CHO) was hydrolysed with cold concentrated hydrochloric acid to give 4-chloro-5-amino-2 : 6-dimethylpyrimidine.


(XVIII.)


(XIX.)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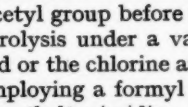
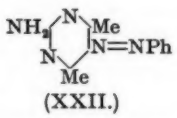

(XXI.)

The introduction of a 5-amino-group into the pyrimidine nucleus by reduction of a 5-benzeneazo-group seemed to offer a suitable approach to the preparation of derivatives of 2 : 5-diaminopyrimidine such as (V) and (VI). Since direct coupling of a pyrimidine with a diazonium compound requires the presence of groups capable of taking part in a prototropic change in at least two positions adjacent to the nuclear nitrogen atoms (Lythgoe, Todd, and Topham, *J.*, 1944, 315), the azo-group could not be introduced directly in the present case. 2-*Amino*-5-*benzeneazo*-4 : 6-*dimethylpyrimidine* (XXII) was readily prepared, however, by the

condensation of benzeneazoacetylacetone (Bülow *et al.*, *Ber.*, 1902, **35**, 2188) with guanidine; on catalytic hydrogenation 2 : 5-*diamino*-4 : 6-*dimethylpyrimidine* (XXIII) was obtained. Alkylation of the diamine with β-diethylaminoethyl chloride afforded (V; R = $[CH_2]_2NEt_2$). That alkylation occurred at the 5-amino-group is shown by the non-identity of the product with 5-amino-2-β-diethylaminoethylamino-4 : 6-dimethylpyrimidine (VI; R = $[CH_2]_2{\cdot}NEt_2$), the synthesis of which is described below.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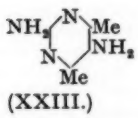
(XXIII.)

Several methods of approach to the synthesis of compounds of type (VI) were excluded by the failure of benzeneazoacetylacetone to condense under a variety of conditions with urea, thiourea, *S*-methyl*iso*thiourea, or β-diethylaminoethylguanidine. The last-named compound, obtained as the *hydriodide* by the interaction of *S*-methyl*iso*thiourea hydriodide with β-diethylaminoethylamine, also failed to give the expected product (XIII; R = $[CH_2]_2{\cdot}NEt_2$) on reaction with ethyl α-methylacetoacetate. The substance (VI; R = $[CH_2]_2{\cdot}NEt_2$) was finally obtained by applying the method employed by Adams and Whitmore (*J. Amer. Chem. Soc.*, 1945, **67**, 736) for the alkylation of 2-aminopyrimidines. 2-Amino-5-benzeneazo-4 : 6-dimethylpyrimidine (XXII) was converted into its sodium salt by treatment with sodamide in toluene; reaction with β-diethylaminoethyl chloride then gave 2-β-*diethylaminoethylamino*-5-*benzeneazo*-4 : 6-*dimethylpyrimidine*, which on catalytic hydrogenation yielded the desired compound (VI).

Attempts to prepare compounds of type (VII) by the alkylation of 4 : 5-diamino-2 : 6-dimethylpyrimidine (Andersag and Westphal, *loc. cit.*) led to unsatisfactory results. The diamine reacted with dialkylaminoalkyl chlorides, but the products could not be obtained in an analytically pure condition and gave no crystalline derivatives. A similar result was obtained when β-diethylaminoethyl chloride was brought into reaction with 5-amino-4-hydroxy-2 : 6-dimethylpyrimidine and treatment of the impure reaction product with phosphoryl chloride gave none of the desired chloropyrimidine (XIX; R = $[CH_2]_2{\cdot}NEt_2$).

Experimental.

2-*Amino*-4-*hydroxy*-5-*methylpyrimidine*.—A mixture of ethyl formate (200 g.; 2·7 mols.) and ethyl propionate (255 g.; 2·5 mols.) was added dropwise to a well stirred suspension of powdered sodium (52·5 g.; 2·3 atoms) in anhydrous ether (1250 c.c.) during 3 hours. After being left overnight the crude ethyl sodio-α-formylpropionate was collected, washed with ether, and suspended in alcohol (1 l.). Guanidine hydrochloride (159 g.; 1·65 mols.) was added and the mixture stirred for 3 hours at room temperature, refluxed for 4 hours, and set aside overnight. The solid was collected and the filtrate evaporated; the residue and the solid were combined, dissolved in warm water and made alkaline with sodium hydroxide. The cooled, filtered solution was acidified with acetic acid and the product collected and crystallised from water. 2-Amino-4-hydroxy-5-methylpyrimidine (36·5 g.; 17%) formed colourless needles, m. p. 277—279°. Johnson and Clapp (*loc. cit.*) give m. p. 320—321°. Payman (M.Sc. Thesis, Manchester University, 1943, p. 86) gives m. p. 278—280° (Found: C, 48·0; H, 5·5; N, 33·0. Calc. for $C_5H_7ON_3$: C, 48·0; H, 5·6; N, 33·6%).

4-*Chloro*-2-*amino*-5-*methylpyrimidine*.—A mixture of 2-amino-4-hydroxy-5-methylpyrimidine (5 g.) and phosphoryl chloride (30 c.c.) was refluxed for 45 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue poured on ice and left for 24 hours. On making alkaline with ammonia, keeping the temperature below 10°, 4-*chloro*-2-*amino*-5-*methylpyrimidine* (3·95 g.; 68%) precipitated as a colourless solid, m. p. 177—180°. Recrystallisation from alcohol gave colourless needles, m. p. 184—185° (Found: C, 42·2; H, 4·3; N, 29·3. $C_5H_6N_3Cl$ requires C, 41·8; H, 4·2; N, 29·3%).

2-*Amino*-4-β-*diethylaminoethylamino*-5-*methylpyrimidine*.—4-Chloro-2-amino-5-methylpyrimidine (3·5 g.) was treated with β-diethylaminoethylamine (11·4 g.) by the general method described in Part III (*loc. cit.*). The product (4·7 g.; 87%) distilled at 170° (bath temp.)/3 × 10^{-4} mm. as a viscous straw-coloured oil. The *dipicrate* formed yellow prisms from alcohol, m. p. 195—196° (Found: C, 41·0; H, 3·7; N, 22·4. $C_{11}H_{21}N_5{,}2C_6H_3O_7N_3$ requires C, 40·5; H, 3·9; N, 22·6%).

2-*Amino*-4-γ-*diethylaminopropylamino*-5-*methylpyrimidine*.—A mixture of 4-chloro-2-amino-5-methylpyrimidine (4 g.) and γ-diethylaminopropylamine (14·5 g.) was refluxed for 5 hours. The *product*, isolated in the usual manner, distilled at 185—210° (bath temp.)/4 × 10^{-4} mm. as an oil which crystallised on standing with anhydrous ether for 5 days. Recrystallisation from light petroleum (b. p. 60—80°) gave colourless needles, m. p. 70—71° (Found: C, 60·8; H, 9·7; N, 29·4. $C_{12}H_{23}N_5$ requires C, 60·8; H, 9·7; N, 29·5%).

2-*Amino*-4-*hydroxy*-5-*phenoxypyrimidine*.—A mixture of ethyl formate (37 g.; 0·5 mol.) and ethyl phenoxyacetate (90 g.; 0·5 mol.) was added dropwise to a cooled and stirred suspension of powdered sodium (11·5 g.; 0·5 mol.) in anhydrous ether (250 c.c.) during 45 minutes. After standing overnight, the crude ethyl sodio-α-formyl-α-phenoxyacetate was collected, washed with ether and added to a

mixture of guanidine hydrochloride (47·8 g.; 0·5 mol.) and alcoholic sodium ethoxide (from 11·5 g. of sodium and 200 c.c. of alcohol). The mixture was refluxed for 5 hours and cooled, the precipitate collected, and the filtrate evaporated to dryness. The combined solids were dissolved in warm water, filtered, cooled, and acidified with acetic acid. The precipitate, m. p. 247—250°, was purified by redissolving in alkali (charcoal) and reprecipitating with acetic acid: the resulting *2-amino-4-hydroxy-5-phenoxypyrimidine* (56 g.; 55%), recrystallised from water, gave colourless prisms, m. p. 255—256° (Found: C, 59·2; H, 4·8; N, 20·9. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·4; N, 20·7%).

4-Chloro-2-amino-5-phenoxypyrimidine.—A mixture of finely powdered 2-amino-4-hydroxy-5-phenoxypyrimidine (5 g.) and phosphoryl chloride (30 c.c.) was refluxed for 15 minutes. Worked up in the usual manner the solid product (4·4 g.) had m. p. 134—137°. A specimen purified by sublimation in a vacuum and recrystallisation from alcohol yielded *4-chloro-2-amino-5-phenoxypyrimidine* as needles, m. p. 157·5° (Found: C, 54·4; H, 3·2; N, 18·7. $C_{10}H_8ON_3Cl$ requires C, 54·2; H, 3·6; N, 18·9%).

Acetylation of 2-Amino-4-hydroxy-5-phenoxypyrimidine.—A mixture of the pyrimidine (3 g.), acetic anhydride (1·53 c.c.), and anhydrous pyridine (15 c.c.) was refluxed for 2 hours. Alcohol (7 c.c.) was added to the cooled mixture and the solid (2·05 g.), m. p. 239—240°, which separated was collected and washed with alcohol. Recrystallisation from alcohol–pyridine gave colourless needles, m. p. 239—240° (Found: C, 60·6; H, 4·7; N, 18·3; *M* (Rast), 478. $C_{24}H_{20}O_5N_6$ requires C, 60·9; H, 4·2; N, 17·9%; *M*, 472). The *substance* was soluble in hot water, alcohol, and pyridine. It dissolved in cold aqueous sodium hydroxide and was reprecipitated unchanged on acidification.

4-Chloro-2-acetamido-5-phenoxypyrimidine.—The above substance (13·3 g.) was refluxed with phosphoryl chloride (80 c.c.) for 15 minutes. The product (13·5 g.), isolated in the usual manner, was an orange solid, m. p. 148—153°. After recrystallising twice from alcohol (charcoal), *4-chloro-2-acetamido-5-phenoxypyrimidine* formed almost colourless needles, m. p. 163° (Found: C, 55·0; H, 3·7; N, 15·7. $C_{12}H_{10}O_2N_3Cl$ requires C, 54·7; H, 3·8; N, 15·9%).

2-Amino-4-β-diethylaminoethylamino-5-phenoxypyrimidine.—A mixture of 4-chloro-2-acetamido-5-phenoxypyrimidine (1·5 g.) and β-diethylaminoethylamine (2·65 g.) was refluxed for 5 hours and excess of diamine removed under reduced pressure. The residual oil was refluxed with dilute hydrochloric acid (30 c.c. of 10%) for 6 hours. The cooled solution was made alkaline and the liberated oil isolated by extraction with ether. *2-Amino-4-β-diethylaminoethylamino-5-phenoxypyrimidine* (1·52 g.; 89%) distilled at 200° (bath temp.)/10^{-4} mm. as a yellow viscous oil, and then crystallised from benzene–light petroleum in colourless platelets, m. p. 114—115° (Found: C, 63·8; H, 7·5; N, 23·6. $C_{14}H_{23}ON_5$ requires C, 63·8; H, 7·6; N, 23·2%).

2-Amino-4-γ-diethylaminopropylamino-5-phenoxypyrimidine.—Prepared from 4-chloro-2-acetamido-5-phenoxypyrimidine (1·1 g.) and γ-diethylaminopropylamine (2·18 g.) in the manner described above, *2-amino-4-γ-diethylaminopropylamino-5-phenoxypyrimidine* distilled at 250° (bath temp.)/10^{-4} mm. as a yellow, viscous oil (1·3 g.; 98%), which crystallised from benzene–light petroleum as fine needles, m. p. 130·5—131° (Found: C, 65·0; H, 7·9; N, 22·3. $C_{17}H_{25}ON_5$ requires C, 64·8; H, 7·9; N, 22·2%).

5-Bromo-2-amino-4-hydroxy-6-methylpyrimidine.—Bromine (17 c.c.; 0·34 mol.) was added dropwise to a stirred suspension of 2-amino-4-hydroxy-6-methylpyrimidine (40 g.; 0·32 mol.) in acetic acid (350 c.c.) during 30 minutes. After a further 30 minutes the pale yellow hydrobromide, m. p. 250° (decomp.) (93 g.; 100%), was collected and dried at 100°. Recrystallisation from water hydrolysed the salt, giving 5-bromo-2-amino-4-hydroxy-6-methylpyrimidine, m. p. 250° (decomp.) (Found: C, 29·4; H, 2·8; N, 20·4. Calc. for $C_5H_6ON_3Br$: C, 29·4; H, 2·9; N, 20·6%). Jaeger (*Annalen*, 1891, **262**, 367) prepared the substance but gave no m. p.

4-Chloro-5-bromo-2-amino-6-methylpyrimidine.—A mixture of the above hydroxypyrimidine hydrobromide (93 g.) and phosphoryl chloride (465 c.c.) was refluxed for 5 hours. The product (58 g.; 79%), isolated in the usual manner, was a yellow solid, m. p. 190—198°. On recrystallisation from alcohol, *4-chloro-5-bromo-2-amino-6-methylpyrimidine* formed colourless needles, m. p. 206—207° (Found: C, 26·8; H, 2·5; N, 19·4. $C_5H_5N_3ClBr$ requires C, 27·0; H, 2·2; N, 18·9%).

5-Bromo-2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine.—A mixture of 4-chloro-5-bromo-2-amino-6-methylpyrimidine (2·23 g.; 0·01 mol.), β-diethylaminoethylamine (1·17 g.; 0·01 mol.) and β-ethoxyethanol (20 c.c.) was refluxed for 5 hours. After removal of the solvent under reduced pressure the product was isolated in the usual manner. *5-Bromo-2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine* (2·4 g.; 80%) distilled at 200° (bath temp.)/10^{-2} mm. as a yellow viscous oil (Found: C, 44·0; H, 6·5; N, 23·3. $C_{11}H_{20}N_5Br$ requires C, 43·7; H, 6·6; N, 23·2%).

5-Bromo-2-amino-4-γ-diethylaminopropylamino-6-methylpyrimidine.—4-Chloro-5-bromo-2-amino-6-methylpyrimidine (5 g.; 0·022 mol.) and γ-diethylaminopropylamine (11·7 g.; 0·089 mol.) were heated together under reflux for 6 hours. The product (6·5 g.; 91·5%), isolated in the usual manner, distilled at 220—235° (bath temp.)/2×10^{-4} mm. as a yellow viscous oil which slowly crystallised. On recrystallisation from light petroleum, *5-bromo-2-amino-4-γ-diethylaminopropylamino-6-methylpyrimidine* formed colourless needles, m. p. 105·5—107° (Found: C, 45·6; H, 7·0; N, 22·3. $C_{13}H_{22}N_5Br$ requires C, 45·5; H, 6·9; N, 22·1%).

4-Chloro-2:6-diaminopyrimidine.—4:6-Dichloro-2-aminopyrimidine (70 g.), prepared by the interaction of 2-amino-4:6-dihydroxypyrimidine (Michael, *J. pr. Chem.*, 1894, **49**, 35) and phosphoryl chloride as indicated by Büttner (*loc. cit.*), was heated with alcoholic ammonia (420 c.c., saturated at 0°) in an autoclave at 150° for 3 hours. The solid was collected, combined with the residue obtained by evaporating the filtrate, and recrystallised from water (charcoal), giving colourless needles (51·5 g.; 84%), m. p. 196·5—197·5° (Büttner gives m. p. 198°).

2:6-Diamino-4-β-diethylaminoethylaminopyrimidine.—A solution of 4-chloro-2:6-diaminopyrimidine (5·78 g.; 0·04 mol.) and β-diethylaminoethylamine (4·45 g.; 0·043 mol.) in dry pyridine (13 c.c.) was refluxed for 16 hours and worked up in the usual way. The chloroform solution of the crude product on standing deposited unchanged 4-chloro-2:6-diaminopyrimidine (0·62 g.), which was removed; distillation of the filtrate gave 2:6-diamino-4-β-diethylaminoethylaminopyrimidine (5·5 g.; 62%), b. p. 270° (bath temp.)/10^{-3} mm., as a pale yellow oil. The *dipicrate*, rosettes of needles from water, had

m. p. 204—206° (Found: C, 39·0; H, 4·1; N, 25·0. $C_{10}H_{20}N_6,2C_6H_3O_7N_3$ requires C, 38·7; H, 3·8; N, 24·6%).

2 : 6-*Diamino*-4-*γ-diethylaminopropylaminopyrimidine*.—This, prepared in a similar manner, was a viscous yellow oil, b. p. 250° (bath temp.)/10^{-3} mm.; the *dipicrate* formed rosettes of needles from water, m. p. 202—203° (Found: C, 39·5; H, 4·3; N, 24·1. $C_{11}H_{22}N_6,2C_6H_3O_7N_3$ requires C, 39·6; H, 4·0; N, 24·1%).

2-*Amino*-4 : 6-*bis*-(*β-diethylaminoethylamino*)*pyrimidine*.—(*a*) 4-Chloro-2 : 6-diaminopyrimidine (6·5 g.; 0·045 mol.) and β-diethylaminoethylamine (20·8 g.; 0·18 mol.) were heated under reflux for 6 hours. Isolation of the product in the usual manner gave a brown viscous oil (9·25 g.), b. p. 230° (bath temp.)/10^{-3} mm., which on extraction with light petroleum yielded a colourless, hygroscopic, waxy solid, m. p. 45—47°. Recrystallisation from light petroleum raised the m. p. of the *compound* to 58—60° (Found: C, 59·6; H, 10·5; N, 30·1. $C_{16}H_{33}N_7$ requires C, 59·5; H, 10·2; N, 30·3%). The picrate had m. p. 177·5—178·5°.

(*b*) 4-Chloro-2-amino-6-β-diethylaminoethylaminopyrimidine (1·0 g.; 0·004 mol.) (Curd, *et al.*, forthcoming publication) was treated with β-diethylaminoethylamine (0·95 g.; 0·008 mol.) at 150° for 6 hours. The product, distilled at 260° (bath temp.)/5 × 10^{-3} mm. and twice crystallised from light petroleum, was a hygroscopic, waxy solid, m. p. 51—55°. The picrate had m. p. 178°, undepressed in admixture with the picrate obtained by method (*a*).

2-*Amino*-4 : 6-*bis*-(*γ-diethylaminopropylamino*)*pyrimidine*.—Prepared from 4-chloro-2 : 6-diaminopyrimidine (5·0 g.; 0·034 mol.) and γ-diethylaminopropylamine (17·0 g.; 0·13 mol.) by method (*a*) above, the *substance* was a brown viscous oil (5·65 g.), b. p. 270° (bath temp.)/4 × 10^{-4} mm., which could not be obtained crystalline. It was redistilled for analysis (Found: C, 62·1; H, 10·6; N, 28·2. $C_{18}H_{37}N_7$ requires C, 61·6; H, 10·5; N, 27·9%).

4 : 6-*Dichloro*-2-*amino*-5-*methylpyrimidine*.—The following modification of the method of Gerngross (*Ber.*, 1905, **38**, 3394) gave satisfactory results. To a solution of sodium ethoxide (4·0 mols.) in alcohol (1300 c.c.) were added successively guanidine hydrochloride (191 g.; 2·0 mols.) and ethyl methylmalonate (348 g.; 2·0 mols.). After the mixture had been refluxed for 2 hours and left overnight, the precipitated sodium salt was collected, combined with the residue obtained by evaporating the filtrate, dissolved in warm water, and treated with charcoal. The filtered solution was acidified with acetic acid, and the precipitated 2-amino-4 : 6-dihydroxy-5-methylpyrimidine (243 g.; 86%), m. p. > 300°, was collected, washed with water and dried at 100°. A mixture of this (125 g.) and phosphoryl chloride (500 c.c.) was refluxed for 45 minutes, excess of reagent removed by distillation, and the residue poured on ice and left overnight. The product (129 g.), precipitated by addition of ammonia with cooling, was collected and dried at 100°; m. p. 227—237°. Sublimation in a vacuum gave 94 g., m. p. 243·5—246°; washing with water and then methanol raised the m. p. to 245—248° (Gerngross, *loc. cit.*, gives m. p. 249°). Yield, 89 g.; 56·5%.

4-*Chloro*-2 : 6-*diamino*-5-*methylpyrimidine*.—This was prepared from 4 : 6-dichloro-2-amino-5-methylpyrimidine in 87% yield by the method of Gerngross (*loc. cit.*).

2 : 6-*Diamino*-4-*β-diethylaminoethylamino*-5-*methylpyrimidine*.—Prepared in the usual manner the *base* distilled at 250° (bath temp.)/10^{-4} mm. as a viscous, straw-coloured oil (yield 88%), which crystallised on trituration with dry ether at 0°. Recrystallisation from benzene–light petroleum gave rosettes of colourless needles, m. p. 102° (Found: C, 55·0; H, 9·2; N, 35·2. $C_{11}H_{22}N_6$ requires C, 55·5; H, 9·2; N, 35·3%).

2 : 6-*Diamino*-4-*γ-diethylaminopropylamino*-5-*methylpyrimidine*.—A viscous yellow oil, b. p. 250—270° (bath temp.)/10^{-3} mm. (yield, 81%), which was converted by trituration with ether to a hygroscopic, waxy solid. The *bis*-3 : 5-*dinitrobenzoate* formed needles from aqueous alcohol, m. p. 213° (Found: C, 45·8; H, 4·8; N, 20·2. $C_{12}H_{24}N_6,2C_7H_4O_6N_2$ requires C, 46·2; H, 4·7; N, 20·7%).

4-*Chloro*-2-*amino*-6-*β-diethylaminoethylamino*-5-*methylpyrimidine*.—A solution of 4 : 6-dichloro-2-amino-5-methylpyrimidine (8·9 g.; 0·05 mol.) and β-diethylaminoethylamine (5·8 g.; 0·05 mol.) in pyridine (25 c.c.) was refluxed for 15 hours, pyridine removed by distillation, and the residue dissolved in dilute hydrochloric acid. The product was liberated by the addition of solid sodium hydroxide, keeping the temperature below 10°, and extracted with chloroform. After distillation at 250° (bath temp.)/10^{-4} mm. and crystallisation from ethyl acetate–light petroleum, 4-*chloro*-2-*amino*-6-*β-diethylaminoethylamino*-5-*methylpyrimidine* (7·1 g.; 55%) formed colourless needles, m. p. 99—101° (Found: C, 50·8; H, 7·6; N, 27·2. $C_{11}H_{20}N_5Cl$ requires C, 51·3; H, 7·8; N, 27·2%).

4-*Chloro*-2-*amino*-6-*γ-diethylaminopropylamino*-5-*methylpyrimidine*.—A mixture of 4 : 6-dichloro-2-amino-5-methylpyrimidine (8·9 g.; 0·05 mol.), γ-diethylaminopropylamine (6·5 g.; 0·05 mol.), and glacial acetic acid (2·85 c.c.; 0·05 mol.) was heated at 110° for 4 hours and at 130° for a further 2 hours. After cooling, the mixture was diluted with ice-water (40 c.c.) and made alkaline with ammonia. After 2 days, a small amount of unchanged dichloropyrimidine was removed by filtration and the *product* precipitated as a colourless solid (10·3 g.; 76%), m. p. 112—114°, by adding solid sodium hydroxide. Recrystallisation from ethyl acetate gave colourless needles, m. p. 121—122° (Found: C, 53·0; H, 8·0; N, 25·8. $C_{12}H_{22}N_5Cl$ requires C, 53·0; H, 8·1; N, 25·8%).

4-*Hydroxy*-2-*methylthio*-5 : 6-*dimethylpyrimidine* (X).—*S*-Methyl*iso*thiourea hydriodide (21·7 g.; 0·1 mol.) was added to alcoholic sodium ethoxide (from 4·6 g. of sodium and 250 c.c. of alcohol), followed after 10 minutes by ethyl α-methylacetoacetate (14·4 g.; 0·1 mol.). Next day, the alcohol was removed under reduced pressure and the residue dissolved in water. The solution was made just acid by adding hydrochloric acid, and the colourless precipitate was collected, washed with water, and recrystallised from alcohol giving colourless plates (10·3 g.; 61%), m. p. 227—229° (Chi and Kao, *loc. cit.*, give m. p. 225—227°) (Found: C, 49·5; H, 6·1; N, 16·5. Calc. for $C_7H_{10}ON_2S$: C, 49·4; H, 5·9; N, 16·5%).

4-*Chloro*-2-*methylthio*-5 : 6-*dimethylpyrimidine* (XI).—A mixture of 4-hydroxy-2-methylthio-5 : 6-dimethylpyrimidine (11 g.) and phosphoryl chloride (150 c.c.) was warmed on the steam-bath for 5 minutes, excess of phosphoryl chloride removed under reduced pressure, and the residue poured on ice; the white precipitate was recrystallised from aqueous alcohol. 4-*Chloro*-2-*methylthio*-5 : 6-*dimethyl*-

pyrimidine (11·2 g.; 92%) formed colourless needles, m. p. 35—36° (Found: C, 44·1; H, 4·5; N, 14·7. $C_7H_9N_2ClS$ requires C, 44·6; H, 4·8; N, 14·8%).

4-*Amino*-2-*methylthio*-5 : 6-*dimethylpyrimidine* (XII).—The above chloro-compound (2·05 g.) was dissolved in excess of saturated anhydrous alcoholic ammonia and the solution was heated in an autoclave at 115—125° for 6 hours. Ammonium chloride was removed by filtration and the filtrate evaporated to dryness. Recrystallised from hot water (charcoal) the residue gave 4-*amino*-2-*methylthio*-5 : 6-*dimethylpyrimidine* (0·9 g.; 50%) as colourless prisms, m. p. 158—159·5° (Found: C, 49·7; H, 6·3; N, 24·8. $C_7H_{11}N_3S$ requires C, 49·7; H, 6·5; N, 24·9%).

4-*Amino*-2-γ-*diethylaminopropylamino*-5 : 6-*dimethylpyrimidine*.—A mixture of 4-amino-2-methylthio-5 : 6-dimethylpyrimidine (5·6 g.; 0·033 mol.) and γ-diethylaminopropylamine (8·6 g.; 0·066 mol.) was heated in an autoclave at 200—210° for 22 hours. After removal of excess of amine by distillation, the residue was distilled at 5 × 10^{-4} mm. (bath temp. 170—175°). The distillate, a pale yellow, viscous oil, contained sulphur. On heating at 100°/10^{-4} mm. for several hours, some unchanged methylthio-compound sublimed; the remainder of the starting material was removed by two further distillations, the first fractions of distillate being rejected. The final *product* (3·25 g.; 39%) was a viscous oil which did not crystallise (Found: C, 61·4; H, 9·7; N, 27·7. $C_{13}H_{25}N_5$ requires C, 62·1; H, 10·0; N, 27·9%). The *bis*-3 : 5-*dinitrobenzoate* separated from alcohol as pale yellow prisms, m. p. 210—212° (Found: C, 47·4; H, 4·7; N, 18·6. $C_{13}H_{25}N_5,2C_7H_4O_6N_2$ requires C, 48·0; H, 4·9; N, 18·7%).

2-β-*Diethylaminoethylamino*-4-*hydroxy*-5 : 6-*dimethylpyrimidine*.—A mixture of 4-hydroxy-2-methylthio-5 : 6-dimethylpyrimidine (5·7 g.; 0·033 mol.) and β-diethylaminoethylamine (4·3 g.; 0·036 mol.) was heated under reflux in an oil-bath at 160—170° for 3 hours. The product distilled at 240—250° (bath temp.)/4 × 10^{-3} mm. as a pale yellow oil (7·75 g.; 98%). It crystallised on trituration with light petroleum; on recrystallisation from the same solvent, 2-β-*diethylaminoethylamino*-4-*hydroxy*-5 : 6-*dimethylpyrimidine* had m. p. 86·5—88° (Found: C, 60·5; H, 9·6; N, 23·9. $C_{13}H_{23}ON_4$ requires C, 60·5; H, 9·2; N, 23·5%).

4-*Chloro*-2-β-*diethylaminoethylamino*-5 : 6-*dimethylpyrimidine*.—A mixture of the above hydroxypyrimidine (7·0 g.) and phosphoryl chloride (20 c.c.) was heated gradually to boiling; a vigorous reaction then occurred. After 5 minutes the mixture was cooled rapidly and poured on ice. Worked up in the usual manner 4-*chloro*-2-β-*diethylaminoethylamino*-5 : 6-*dimethylpyrimidine* (6·15 g.; 81%) distilled at 140—150° (bath temp.)/2 × 10^{-4} mm. as a pale yellow oil which rapidly solidified. A sample was further purified by sublimation at 90°/10^{-4} mm. and had m. p. 46·5—47·5° (Found: C, 55·6; H, 8·0; N, 22·1. $C_{13}H_{21}N_4Cl$ requires C, 56·1; H, 8·2; N, 21·8%).

4-*Amino*-2-β-*diethylaminoethylamino*-5 : 6-*dimethylpyrimidine*.—(*a*) A solution of the above chloropyrimidine (5·5 g.) in excess of saturated alcoholic ammonia was heated in an autoclave at 180—190° for 3 hours. The crude product distilled at 180—190° (bath temp.)/8 × 10^{-3} mm. as a nearly colourless viscous oil which rapidly crystallised. On recrystallisation from benzene, 4-*amino*-2-β-*diethylaminoethylamino*-5 : 6-*dimethylpyrimidine* (2·45 g.; 49%) was obtained as colourless prisms, m. p. 130—131·5° (Found: C, 60·9; H, 9·5; N, 29·3. $C_{13}H_{23}N_5$ requires C, 60·8; H, 9·7; N, 29·5%).

(*b*) 4-Amino-2-methylthio-5 : 6-dimethylpyrimidine (0·85 g.; 0·005 mol.) and β-diethylaminoethylamine (2·3 g.; 0·02 mol.) were mixed and heated in an autoclave at 190—200° for 22 hours. Distillation of the crude product gave a thick yellow oil, b. p. 200° (bath temp.)/2 × 10^{-3} mm., which rapidly solidified, melted indefinitely at about 140°, and appeared to be a mixture of starting material and the desired product. After recrystallising five times from benzene the final product (0·15 g.) had m. p. 130—131° and was identical with that obtained by method (*a*).

2-γ-*Di*-n-*butylaminopropylamino*-4-*hydroxy*-5 : 6-*dimethylpyrimidine*.—4-Hydroxy-2-methylthio-5 : 6-dimethylpyrimidine (5·7 g.; 0·033 mol.) was heated with γ-di-*n*-butylaminopropylamine (7·7 g.; 0·041 mol.) at 160—170° for three hours, and the product purified by distillation. It distilled at 260—280° (bath temp.)/2 × 10^{-4} mm. as a pale yellow oil, which slowly solidified (9·9 g.; 96%). The *dipicrate*, crystallised from ethyl alcohol, had m. p. 199—202° (Found: C, 45·6; H, 4·8; N, 19·0. $C_{17}H_{33}ON_4,2C_6H_3O_7N_3$ requires C, 45·4; H, 5·0; N, 18·3%)

4-*Chloro*-2-γ-*di*-n-*butylaminopropylamino*-5 : 6-*dimethylpyrimidine*.—The above hydroxypyrimidine (6·5 g.) was refluxed with phosphoryl chloride (15 c.c.) for 5 mins., and ethyl acetate was used in place of ether for the extraction of the product. The product distilled at 185—190° (bath temp.)/4 × 10^{-3} mm. as a colourless mobile oil which did not crystallise. The *dipicrate* crystallised from alcohol as bright yellow needles, m. p. 167·5—168·5° (Found: C 44·3; H 4·6; N 18·0. $C_{17}H_{31}N_4Cl,2C_6H_3O_7N_3$ requires C, 44·4; H, 4·7; N, 17·8%).

4-*Amino*-2-γ-*di*-n-*butylaminopropylamino*-5 : 6-*dimethylpyrimidine*.—The above chloropyrimidine (3·3 g.) was heated with alcoholic ammonia at 200° for 4 hours and the product was isolated in the usual manner. 4-*Amino*-2-γ-*di*-n-*butylaminopropylamino*-5 : 6-*dimethylpyrimidine* (2·3 g.; 74%) distilled at 210—220° (bath temp.)/2 × 10^{-3} mm. as a viscous yellow oil which did not crystallise (Found: C, 66·2; H, 10·3; N, 22·8. $C_{17}H_{33}N_5$ requires C, 66·5; H, 10·7; N, 22·8%). The *dipicrate* formed yellow prisms from alcohol, m. p. 167—169° (depressed to 145° on admixture with the dipicrate of the corresponding chloropyrimidine) (Found: C, 46·0; H, 5·3; N, 19·9. $C_{17}H_{33}N_5,2C_6H_3O_7N_3$ requires C, 45·5; H, 5·1; N, 20·1%).

2-γ-*Dimethylaminopropylamino*-4-*hydroxy*-5 : 6-*dimethylpyrimidine*.—Prepared from 4-hydroxy-2-methylthio-5 : 6-dimethylpyrimidine (4·25 g.; 0·025 mol.) and γ-dimethylaminopropylamine (2·8 g.; 0·028 mol.) in the usual manner, 2-γ-*dimethylaminopropylamino*-4-*hydroxy*-5 : 6-*dimethylpyrimidine* distilled at 230—235° (bath temp.)/2 × 10^{-2} mm. as a pale yellow oil (5·4 g.; 97%) which set to a waxy solid. A specimen was crystallised from light petroleum as a colourless powder, m. p. 113·5—115° (Found: C, 52·7; H, 8·8; N, 22·7. $C_{11}H_{20}ON_4,1\frac{1}{2}H_2O$ requires C, 52·6; H, 9·2; N, 22·3%).

4-*Chloro*-2-γ-*dimethylaminopropylamino*-5 : 6-*dimethylpyrimidine*.—The above hydroxypyrimidine (16·8 g.) was treated with phosphoryl chloride (40 c.c.) in the usual manner. The *product* distilled at 150—155° (bath temp.)/2 × 10^{-2} mm. as a colourless oil (10 g.; 55%) which rapidly solidified. A

specimen was sublimed at 80—90°/10^{-4} mm. and had m. p. 36—38° (Found: C, 54·4; H, 8·0; N, 22·4. $C_{11}H_{16}N_4Cl$ requires C, 54·4; H, 7·8; N, 23·1%).

4-Amino-2-γ-dimethylaminopropylamino-5 : 6-dimethylpyrimidine.—The foregoing chloropyrimidine (3·0 g.) was treated with alcoholic ammonia in the usual manner; chloroform was used in place of ether for extracting the product, which distilled at 180—190° (bath temp.)/2 × 10^{-3} mm. as a yellow viscous oil (0·8 g.; 28%) and did not crystallise. The *tartrate* crystallised from 95% alcohol as colourless needles, m. p. 168—171° (Found: C, 44·2; H, 7·3; N, 17·5. $C_{11}H_{21}N_5,C_4H_6O_6,2H_2O$ requires C, 44·0; H, 7·6; N, 17·1%).

4-Amino-2-dialkylaminoalkylamino-6-methylpyrimidines (VIII).—The appropriate 4-chloro-2-dialkylaminoalkylamino-6-methylpyrimidine (Part VI, *loc. cit.*) was treated with excess of alcoholic ammonia in an autoclave at 180—190° for 3 hours (in the case of the γ-dibutylaminopropylamino-compound, at 200—210° for 5 hours), and the product was isolated in the usual manner. The *compound* (VIII; R = $NEt_2{\cdot}[CH_2]_2$) solidified after distillation and was crystallised from anhydrous benzene; the other *products* were viscous oils. The *bis-3 : 5-dinitrobenzoates* were crystallised from alcohol. The properties and analyses of the substances are recorded in Table III. The preparation of 4-chloro-2-γ-dimethylaminopropylamino-6-methylpyrimidine and its reaction with ammonia both gave poor yields, and the method described below was therefore preferred.

TABLE III.

4-Amino-2-dialkylaminoalkylamino-6-methylpyrimidines (VIII).

Compound.	M. p.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
VIII, R = $NMe_2{\cdot}[CH_2]_2$	—	$C_{10}H_{19}N_5$	56·7	8·9	—	57·4	9·1	—
,, dinitrobenzoate	223—225°	$C_{10}H_{19}N_5,2C_7H_4O_6N_2$	46·0	4·6	19·3	45·5	4·3	19·9
VIII, R = $NEt_2{\cdot}[CH_2]_2$	98—100	$C_{11}H_{21}N_5$	59·3	9·6	31·8	59·2	9·4	31·4
VIII, R = $NEt_2{\cdot}[CH_2]_3$	—	$C_{12}H_{23}N_5$	60·7	9·6	—	60·8	9·7	—
,, dinitrobenzoate	218—220	$C_{12}H_{23}N_5,2C_7H_4O_6N_2$	47·4	4·8	18·6	47·2	4·7	19·0
VIII, R = $NBu_2{\cdot}[CH_2]_3$	—	$C_{16}H_{31}N_5$	66·2	10·4	23·5	65·5	10·6	23·9
,, dinitrobenzoate	200—202	$C_{16}H_{31}N_5,2C_7H_4O_6N_2$	50·1	5·4	17·3	50·2	5·4	17·6

4-Amino-2-methylthio-6-methylpyrimidine (XVI).—A solution of 4-chloro-2-methylthio-6-methylpyrimidine (4 g.) (Wheeler and McFarland, *loc. cit.*) in excess of concentrated alcoholic ammonia was heated in an autoclave at 125—135° for 5½ hours. Excess of ammonia and alcohol were removed by distillation and the residue was dissolved in hot water. On cooling, *4-amino-2-methylthio-6-methylpyrimidine* (2·6 g.; 74%) separated as colourless plates, m. p. 132—134°, raised on recrystallisation to 133·5—135° (Found: C, 46·2; H, 5·7; N, 26·8. $C_6H_9N_3S$ requires C, 46·5; H, 5·8; N, 27·1%).

4-Amino-2-γ-dimethylaminopropylamino-6-methylpyrimidine.—A mixture of 4-amino-2-methylthio-6-methylpyrimidine (2 g.) and γ-dimethylaminopropylamine (2·6 g.) was heated in an autoclave at 160—170° for 14 hours. 4-Amino-2-γ-dimethylaminopropylamino-6-methylpyrimidine distilled at 180—200° (bath temp.)/10^{-4} mm. as a pale yellow viscous oil (2·5 g.; 93%), which did not crystallise. The bis-3 : 5-dinitrobenzoate, crystallised from alcohol, formed hygroscopic pale yellow needles, m. p. 223—225°, undepressed by material obtained by the previous method.

6-Amino-4-dialkylaminoalkylamino-2 : 5-dimethylpyrimidines (Type III).—Prepared from 4-chloro-6-amino-2 : 5-dimethylpyrimidine (Huber and Hölscher, *loc. cit.*) and the appropriate amines by the general method described in Part III (*loc. cit.*), and crystallised from light petroleum or benzene–light petroleum. The properties and analyses of these *substances* are given in Table IV.

TABLE IV.

6-Amino-4-dialkylaminoalkylamino-5-methyl- and -2 : 5-dimethyl-pyrimidines (Types III and IX).

Type.	Compound. R.	Appearance.	M. p.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
III	$[CH_2]_2{\cdot}NEt_2$	Needles	82—82·5°	$C_{12}H_{23}N_5$	60·4	9·6	30·1	60·8	9·7	29·5
III	$[CH_2]_3{\cdot}NMe_2$	Waxy,* hygroscopic	89—91	$C_{11}H_{21}N_5$	—	—	—	—	—	—
III	$[CH_2]_3{\cdot}NEt_2$	Needles	99—99·5	$C_{13}H_{25}N_5$	62·0	10·3	27·3	61·2	9·9	27·9
IX	$[CH_2]_2{\cdot}NEt_2$	Needles	95·5—96·5	$C_{12}H_{23}N_5$	58·9	9·9	31·4	59·2	9·4	31·4
IX	$[CH_2]_3{\cdot}NEt_2$	Needles	93—94	$C_{13}H_{25}N_5$	61·1	9·5	29·2	60·8	9·7	29·5

* *Bis-3 : 5-dinitrobenzoate*, needles from alcohol, m. p. 207·5—209° (Found: C, 46·7; H, 4·8; N, 19·8. $C_{11}H_{21}N_5,2C_7H_4O_6N_2$ requires C, 46·4; H, 4·5; N, 19·5%).

4 : 6-Dihydroxy-5-methylpyrimidine.—Formamidine hydrochloride (42 g.; 0·525 mol.) and diethyl methylmalonate (91 g.; 0·525 mols.) were added successively to alcoholic sodium ethoxide (from 24·5 g. of sodium and 360 c.c. of alcohol) at 20—25°. After being kept overnight, the mixture was refluxed for 1 hour, cooled, and filtered. The collected solid was combined with the residue obtained by evaporation of the filtrate, dissolved in warm water (650 c.c.), cooled, and acidified to litmus with acetic acid; *4 : 6-dihydroxy-5-methylpyrimidine* (39·5 g.; 61%) then separated. Recrystallised from water it formed colourless prisms, which decomposed from 320° (Found: C, 48·0; H, 4·8; N, 22·2. $C_5H_6O_2N_2$ requires C, 47·6; H, 4·8; N, 22·2%).

4 : 6-*Dichloro*-5-*methylpyrimidine*.—A mixture of 4 : 6-dihydroxy-5-methylpyrimidine (39 g.) and phosphoryl chloride (200 c.c.) was refluxed for 40 minutes, a clear solution being obtained. On working up 4 : 6-*dichloro*-5-*methylpyrimidine* (34 g.; 66%) crystallised from water in colourless needles, m. p. 56·5—57·5° (Found: C, 36·6; H, 2·4; N, 16·5. $C_5H_4N_2Cl_2$ requires C, 36·8; H, 2·4; N, 17·2%).

4-*Chloro*-6-*amino*-5-*methylpyrimidine*.—A mixture of 4 : 6-dichloro-5-methylpyrimidine (16·3 g.) and alcoholic ammonia (115 c.c., saturated at 0°) was heated at 140° for 3 hours. After evaporation, the residue was crystallised from water; 4-*chloro*-6-*amino*-5-*methylpyrimidine* separated as colourless needles, m. p. 237—238° (Found: C, 42·3; H, 4·4; N, 29·6. $C_5H_6N_3Cl$ requires C, 41·8; H, 4·2; N, 29·3%).

6-*Amino*-4-*dialkylaminoalkylamino*-5-*methylpyrimidines* (Type IX).—Prepared from the above chloropyrimidine in the usual manner, and crystallised from benzene–light petroleum. The properties and analyses of the *compounds* are given in Table IV.

5-*Formamido*-4-*hydroxy*-2 : 6-*dimethylpyrimidine* (XVIII; R = NH·CHO).—5-Amino-4-hydroxy-2 : 6-dimethylpyrimidine (13·5 g.) (Andersag and Westphal, *loc. cit.*) was dissolved in 98% formic acid (75 c.c.), and the solution refluxed for 15 minutes. Excess of formic acid was removed under reduced pressure and the solid residue was dissolved in water. The aqueous solution was evaporated to dryness under reduced pressure and the operation repeated twice to effect complete removal of formic acid. The product was recrystallised from alcohol (charcoal); 5-*formamido*-4-*hydroxy*-2 : 6-*dimethylpyrimidine* (14·8 g.; 92%) formed colourless, felted needles, m. p. 238—239° (decomp.) (Found: C, 50·2; H, 5·4; N, 24·8. $C_7H_9O_2N_3$ requires C, 50·3; H, 5·4; N, 25·1%).

4-*Chloro*-5-*formamido*-2 : 6-*dimethylpyrimidine* (XIX; R = CHO).—5-Formamido-4-hydroxy-2 : 6-dimethylpyrimidine (9 g.) was finely powdered and added to ice-cold phosphoryl chloride (75 c.c.). Dimethylaniline (20 c.c.) was now added to the mixture in portions of 3—4 c.c. with constant shaking; the solid gradually dissolved with evolution of heat and the temperature was kept below 50° by external cooling. When all the solid had dissolved, the brown solution was poured on ice with continual stirring. The resulting clear yellow solution was cooled in an ice-salt mixture and made alkaline by cautious addition of aqueous ammonia, the temperature being kept below 20°. The alkaline liquor was extracted five times with ethyl acetate and the extracts dried and evaporated under reduced pressure. The residue, a mixture of the desired product with dimethylaniline, was treated with cold light petroleum, which precipitated a light yellow solid. Recrystallisation from benzene (charcoal) gave 4-*chloro*-5-*formamido*-2 : 6-*dimethylpyrimidine* (4·5 g.; 45%) as colourless needles, m. p. 158—159·5° (Found: C, 45·0; H, 4·3; N, 22·7. $C_7H_8ON_3Cl$ requires C, 45·2; H, 4·3; N, 22·6%).

4-*Chloro*-5-*amino*-2 : 6-*dimethylpyrimidine* (XIX; R = H).—A solution of 4-chloro-5-formamido-2 : 6-dimethylpyrimidine (3·75 g.) in ice-cold concentrated hydrochloric acid was kept at room temperature for 30 minutes. The solution was cooled in an ice-salt bath and crushed ice was added followed by aqueous ammonia, the temperature being kept below 10°. The bulky white precipitate was collected and recrystallised from a small volume of water (charcoal), giving fine colourless needles (2·7 g.; 85%), m. p. 79—80°, undepressed in admixture with a specimen prepared (in 5% yield) by the method of Andersag and Westphal (*loc. cit.*).

5-*Amino*-4-*dialkylaminoalkylamino*-2 : 6-*dimethylpyrimidines* (IV).—The following substances were prepared by the interaction of 4-chloro-5-amino-2 : 6-dimethylpyrimidine and the appropriate amines, by the general method described in Part III (*loc. cit.*):

5-*Amino*-4-γ-*diethylaminopropylamino*-2 : 6-*dimethylpyrimidine* distilled at 170° (bath temp.)/2×10^{-3} mm. as a yellow oil which soon solidified and was recrystallised from light petroleum. Colourless hygroscopic solid, m. p. 68—70° (yield, 78%) (Found: C, 61·8; H, 9·8; N, 28·0. $C_{13}H_{25}N_5$ requires C, 62·1; H, 9·9; N, 27·8%).

5-*Amino*-4-β-*diethylaminoethylamino*-2 : 6-*dimethylpyrimidine* distilled at 170—180° (bath temp.)/10^{-3} mm. as a pale yellow oil which rapidly crystallised. Recrystallisation from anhydrous benzene–petrol afforded colourless irregular platelets, m. p. 95—96° (yield, 64%) (Found: C, 61·1; H, 9·9; N, 29·5. $C_{12}H_{23}N_5$ requires C, 60·8; H, 9·7; N, 29·5%).

5-*Amino*-4-γ-*di*-n-*butylaminopropylamino*-2 : 6-*dimethylpyrimidine*, b. p. 230—240° (bath temp.)/0·25 mm., was a pale yellow oil which crystallised slowly (yield, 80%) (Found: C, 66·1; H, 11·0; N, 22·3. $C_{17}H_{33}N_5$ requires C, 66·4; H, 10·8; N, 22·8%).

5-*Acetamido*-4-*hydroxy*-2 : 6-*dimethylpyrimidine* (XVIII; R = NHAc).—A solution of 5-amino-4-hydroxy-2 : 6-dimethylpyrimidine (6·2 g.) in acetic anhydride (220 c.c.) was heated on the steam-bath for 30 minutes, then evaporated to dryness under reduced pressure. The residue was added to crushed ice and the resulting clear solution evaporated under reduced pressure. The residue was recrystallised from alcohol, 5-*acetamido*-4-*hydroxy*-2 : 6-*dimethylpyrimidine* (7 g.; 88%) being obtained as a felted mass of colourless needles, m. p. 275° (decomp.), readily soluble in cold water (Found: N, 23·2. $C_8H_{11}O_2N_3$ requires N, 23·2%).

4-*Chloro*-5-*acetamido*-2 : 6-*dimethylpyrimidine* (XIX; R = Ac).—Finely powdered 5-acetamido-4-hydroxy-2 : 6-dimethylpyrimidine (20 g.) was added to phosphoryl chloride (200 c.c.) with shaking. Dimethylaniline (40 c.c.) was added gradually to the mixture with constant shaking, the temperature being kept at 50—60° by cooling in ice; the pyrimidine slowly dissolved. Excess of phosphoryl chloride was removed under reduced pressure and the residue poured on ice. The resulting clear solution was made alkaline with ammonia, the temperature being maintained below 15° during neutralisation, and the liberated product was isolated by extracting five times with chloroform. The extract was dried, evaporated, and the residue recrystallised from benzene (charcoal). 4-*Chloro*-5-*acetamido*-2 : 6-*dimethylpyrimidine* (11·0 g.; 54%) separated as colourless prisms, m. p. 141—142° (Found: C, 48·5; H, 5·1; N, 20·7. $C_8H_{10}ON_3Cl$ requires C, 48·1; H, 5·0; N, 21·0%).

5-*Acetamido*-4-γ-*diethylaminopropylamino*-2 : 6-*dimethylpyrimidine*.—4-Chloro-5-acetamido-2 : 6-dimethylpyrimidine (5 g.; 0·025 mol.) was treated with γ-diethylaminopropylamine (13 g.; 0·1 mol.) by the usual procedure, special care being taken to keep the aqueous solution cool during isolation of the product. 5-*Acetamido*-4-γ-*diethylaminopropylamino*-2 : 6-*dimethylpyrimidine* (6 g.; 74%) distilled at

150—160° (bath temp.)/10^{-4} mm. as a pale yellow mobile oil (Found: C, 59·8; H, 8·7; N, 23·1. $C_{15}H_{27}ON_5$ requires C, 61·4; H, 9·2; N, 23·9%). The *flavianate*, prepared in alcoholic solution, and crystallised thrice from alcohol and once from water, formed bright yellow needles, m. p. 160° after sintering at 98° (Found: C, 47·8; H, 5·7; N, 15·6. $C_{15}H_{27}ON_5,C_{10}H_6O_8N_2S,H_2O$ requires C, 47·9; H, 5·6; N, 15·7. Found in material dried at 100° in a vacuum: C, 48·8; H, 6·0; N, 15·7. $C_{15}H_{27}ON_5,C_{10}H_6O_8N_2S$ requires C, 49·4; H, 5·4; N, 16·1%).

9-*γ-Diethylaminopropyl*-2 : 6 : 8-*trimethylpurine*.—A solution of the foregoing material (5·5 g.) in 30% sulphuric acid (30 c.c.) was heated on the steam-bath for 2 hours; the cooled solution was made alkaline with sodium hydroxide and the liberated oil isolated by extraction with ether. 9-*γ-Diethylaminopropyl*-2 : 6 : 8-*trimethylpurine* distilled at 140—150° (bath temp.)/10^{-4} mm. as a hygroscopic, pale yellow, mobile oil (Found: C, 64·7; H, 9·3. $C_{15}H_{25}N_5$ requires C, 65·5; H, 9·1%). The *dipicrate* formed pale yellow plates from alcohol, m. p. 187—188° (Found: C, 51·7; H, 5·0; N, 22·5. $C_{15}H_{25}N_5,2C_{10}H_8O_8N_4$ requires C, 52·3; H, 5·1; N, 22·7%)

9-*β-Diethylaminoethyl*-2 : 6 : 8-*trimethylpurine*.—The product obtained from the interaction of 4-chloro-5-acetamido-2 : 6-dimethylpyrimidine (9 g.; 0·045 mol.) and β-diethylaminoethylamine (21 g.; 0·18 mol.) was a pale yellow oil, b. p. 130—140° (bath temp.)/2×10^{-3} mm., giving analytical results suggesting it to be a mixture of the expected pyrimidine and the derived purine. It was dissolved in 30% sulphuric acid (40 c.c.) and the solution heated for 3 hours on the steam-bath. On isolation in the usual manner, 9-*β-diethylaminoethyl*-2 : 6 : 8-*trimethylpurine* (9·0 g.; 76%) distilled at 130—135° (bath temp.)/2×10^{-3} mm. as a pale yellow mobile oil (Found: C, 65·0; H, 9·3; N, 26·7. $C_{14}H_{23}N_5$ requires C, 64·3; H, 8·8; N, 26·8%). The *flavianate* crystallised from alcohol in clusters of bright yellow needles, m. p. 248° (decomp.) (Found: C, 50·0; H, 5·1; N, 17·5. $C_{14}H_{23}N_5,C_{10}H_6O_8N_2S$ requires C, 50·1; H, 5·0; N, 17·0%).

9-*γ-Diethylamino-α-methyl*-n-*butyl*-2 : 6 : 8-*trimethylpurine*.—The product of interaction of 4-chloro-5-acetamido-2 : 6-dimethylpyrimidine (1 g.) and γ-diethylamino-α-methyl-*n*-butylamine (4·9 g.) was treated in the manner described in the previous paragraph. 9-*γ-Diethylamino-α-methyl*-n-*butyl*-2 : 6 : 8-*trimethylpurine* (1·3 g.; 85%), b. p. 150—155° (bath temp.)/10^{-4} mm., was an almost colourless oil, from which no crystalline derivative could be obtained (Found: C, 67·1; H, 9·8; N, 22·4. $C_{17}H_{29}N_5$ requires C, 67·6; H, 9·6; N, 23·1%).

2-*Amino*-5-*benzeneazo*-4 : 6-*dimethylpyrimidine* (XXII).—Alcoholic sodium ethoxide (from 5·75 g. of sodium and 100 c.c. of alcohol) was added slowly, with stirring, to a solution of guanidine hydrochloride (23·9 g.; 0·25 mol.) and benzeneazoacetylacetone (51 g.; 0·25 mol.) (Bülow *et al.*, *loc. cit.*) in absolute alcohol (400 c.c.). After 20 days at room temperature the precipitate was collected, washed with water to remove sodium chloride, and crystallised from alcohol. 2-*Amino*-5-*benzeneazo*-4 : 6-*dimethylpyrimidine* (33 g.; 58·5%) formed bright orange plates, m. p. 228—230° (Found: C, 63·4; H, 5·9; N, 30·8. $C_{12}H_{13}N_5$ requires C, 63·5; H, 5·7; N, 30·8%).

2 : 5-*Diamino*-4 : 6-*dimethylpyrimidine* (XXIII).—A solution of the above azo-compound (5 g.) in absolute alcohol was shaken with hydrogen at 90° under a pressure of 75 atmospheres in the presence of palladised barium sulphate until absorption ceased (3 hours). After filtration, the solution was evaporated to dryness under reduced pressure. The residue was washed with ether to remove aniline, and recrystallised from alcohol giving the *compound* as colourless prisms (2·95 g.; 100%), m. p. 183·5—184·5°, which sublimed at 100° in a vacuum (Found: C, 51·8; H, 7·3; N, 40·9. $C_6H_{10}N_4$ requires C, 52·2; H, 7·2; N, 40·6%).

2-*Amino*-5-*β-diethylaminoethylamino*-4 : 6-*dimethylpyrimidine*.—A solution of 2 : 5-diamino-4 : 6-dimethylpyrimidine (8 g.) and β-diethylaminoethyl chloride (19·6 g., freshly distilled) in anhydrous pyridine (40 c.c.) was refluxed for 7 hours. Pyridine was removed under reduced pressure, the dark brown residue dissolved in water and made alkaline, and the precipitated oil isolated by means of ether and distilled. 2-*Amino*-5-*β-diethylaminoethylamino*-4 : 6-*dimethylpyrimidine* (3·6 g.; 26%), b. p. 140—150° (bath temp.)/2×10^{-4} mm., was obtained as a pale yellow oil which rapidly solidified and crystallised from light petroleum in colourless plates, m. p. 95—96·5° (Found: C, 60·6; H, 9·5; N, 29·5. $C_{12}H_{23}N_5$ requires C, 60·8; H, 9·7; N, 29·5%). The *dipicrate* crystallised from acetone as fine yellow needles, m. p. 187—189° (decomp.), depressed to 162—164° in admixture with the dipicrate of 5-amino-2-β-diethylaminoethylamino-4 : 6-dimethylpyrimidine (see below) (Found: N, 21·9. $C_{12}H_{23}N_5,2C_6H_3O_7N_3$ requires N, 22·2%).

2-*β-Diethylaminoethylamino*-5-*benzeneazo*-4 : 6-*dimethylpyrimidine*.—A suspension of sodamide (0·6 g.; 0·015 mol.) and 2-amino-5-benzeneazo-4 : 6-dimethylpyrimidine (1·1 g.; 0·005 mol.) in dry toluene (10 c.c.) was refluxed for 10 hours in a bath at 130°. Ammonia was evolved and the sodium salt of the aminopyrimidine separated. β-Diethylaminoethyl chloride (6·8 g.; 0·05 mol.) was added to the cooled mixture and refluxing was continued for a further 18 hours at 160—170°. The cooled mixture was shaken with dilute hydrochloric acid and the aqueous layer washed with ether and made alkaline. The red oil was isolated by means of ether and distilled at 140° (bath temp.)/10^{-3} mm. The distillate partially crystallised; recrystallisation from light petroleum gave 2-*β-diethylaminoethylamino*-5-*benzeneazo*-4 : 6-*dimethylpyrimidine* (0·95 g.; 58%) as microscopic red leaflets, m. p. 87—88° (Found: C, 66·3; H, 8·1; N, 26·1. $C_{18}H_{23}N_6$ requires C, 66·2; H, 8·0; N, 25·8%).

5-*Amino*-2-*β-diethylaminoethylamino*-4 : 6-*dimethylpyrimidine*.—A solution of the foregoing material (0·8 g.) in alcohol (25 c.c.) was shaken with hydrogen and platinic oxide at room temperature and pressure. Absorption of hydrogen was rapid and the resulting almost colourless solution was filtered and evaporated. The residue distilled at 160° (bath temp.)/2×10^{-3} mm. giving 5-amino-2-β-diethylaminoethylamino-4 : 6-dimethylpyrimidine (0·35 g.; 60%) as a yellow viscous oil. The *dipicrate* crystallised from alcohol in bright yellow needles, m. p. 185—186°, with slight charring from 176°. On admixture with aniline picrate (m. p. 181°) the m. p. was depressed to 151—153° (Found: C, 41·4; H, 4·3; N, 22·3. $C_{12}H_{23}N_5,2C_6H_3O_7N_3$ requires C, 41·5; H, 4·2; N, 22·2%).

β-Diethylaminoethylguanidine Hydriodide.—A solution of *S*-methylisothiourea hydriodide (33 g.; 0·15 mol.) and β-diethylaminoethylamine (18 g.; 0·155 mol.) in alcohol (150 c.c.) was refluxed on the

steam-bath for 2 hours, methylthiol being evolved. The solution was evaporated to dryness and the syrupy residue dissolved in a little water and treated with a slight excess of hydriodic acid (*d* 1·7). After evaporation to dryness the residue was dissolved in warm alcohol and ether added to incipient turbidity. On cooling, *β-diethylaminoethylguanidine dihydriodide* (31·1 g.; 50%) separated as colourless plates, m. p. 136—139°; two further crystallisations raised the m. p. to 140—142° (Found: C, 20·7; H, 4·6; N, 13·7. $C_7H_{20}N_4,2HI$ requires C, 20·3; H, 4·8; N, 13·5%).

Our thanks are due to Imperial Chemical Industries Ltd. (Dyestuffs Division) for grants and gifts of materials and for undertaking the biological testing of the substances described in this paper. We also wish to thank Mr. D. J. Lloyd and Miss B. Thornber for carrying out the majority of the micro-analyses.

UNIVERSITY OF MANCHESTER.
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, April 27th*, 1946.]

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10. *The Synthesis of Some Aryl Pyridyl Sulphones (Arylsulphonylpyridines).*

By H. BURTON and W. A. DAVY.

During an investigation of methods for the synthesis of aryl pyridyl sulphones (or intermediate sulphides) the following routes have been examined: (i) interaction of 4-chloropyridine and sodium *p*-nitrothiophenoxide (cf. Burton and Davy, *J.* 1946, 542); (ii) introduction of the *p*-nitrobenzenesulphenyl (*p*-nitrophenylthio) group into the pyridine nucleus; (iii) interaction of an arylsulphinic acid with a chloropyridine (cf. Roblin, Williams, and Anderson, *J. Amer. Chem. Soc.*, 1941, **63**, 1930). In general, method (iii) was found to be the most satisfactory.

KING and WARE (*J.*, 1939, 875) have shown that methyl iodide reacts rapidly with 4-thiopyridone yielding 4-methylthiopyridine hydriodide. We have investigated the alkylation using ethyl iodide and *n*-octyl bromide. With ethyl iodide ethylation is rapid, but with *n*-octyl bromide no reaction appears to occur in the absence of alkali; in presence of potassium hydroxide the resulting product is non-homogeneous. Comparison with thiophenol and *p*-nitrothiophenol shows that these both react normally in the presence of alkali to give *phenyl* and p-*nitrophenyl octyl sulphide*, respectively. We have already reported (*loc. cit.*) that interaction of 4-thiopyridone and *p*-chloronitrobenzene (I) in presence of alkali is anomalous, leading to 4 : 4′-dinitrodiphenyl sulphide, which presumably arises from the decomposition of 4-thiopyridone to alkali sulphide which then reacts with (I). The alternative route, *viz.*, interaction of 4-chloropyridine (II) and sodium *p*-nitrothiophenoxide (III), has, curiously enough, led to the same abnormal product, although Bambas (*J. Amer. Chem. Soc.*, 1945, **67**, 668) has shown that (III) and 5-bromo-2-nitropyridine interact normally. The mechanism of the reaction whereby 4 : 4′-dinitrodiphenyl sulphide arises from (II) and (III) is not easy to envisage; presumably the SNa group of (III) is partly replaced by chlorine to give (I), which then reacts with unchanged (III).

The use of *p*-nitrobenzenesulphenyl chloride for the introduction of the *p*-nitrophenylthio-group into a reactive molecule is well known (cf. *inter al.*, Zincke, *Annalen*, 1913, **400**, 9; Smiles *et al.*, *J.*, 1931, 2207, 3264; 1932, 1040, 1488; Burton and Hoggarth, *J.*, 1945, 468), but this method does not appear to have been extended to the pyridine series. The reactions with the readily available ethyl 4 : 6-dihydroxy-2-methylpyridine-5-carboxylate (for constitution see Späth and Koller, *Ber.*, 1925, **58**, 2124) and 4 : 6-dihydroxy-2-methylpyridine were studied, the former in some detail. The insolubility of the dihydroxymethylpyridine in the usual inert solvents was a great disadvantage, since the reaction did not proceed satisfactorily in a non-homogeneous phase. In hot nitrobenzene–chloroform the sulphenyl chloride and the ester interacted smoothly, and the expected *ethyl* 4 : 6-*dihydroxy*-3-p-*nitrophenylthio*-2-*methylpyridine*-5-*carboxylate* was obtained. This was characterised by acid hydrolysis to 4 : 6-*dihydroxy*-3-p-*nitrophenylthio*-2-*methylpyridine* (IV); formation of this showed the absence of the p-$NO_2{\cdot}C_6H_4{\cdot}S{\cdot}N<$ grouping, which could arise from the pyridone form of the original ester. The *p*-nitrophenylthio-ester was also characterised by the preparation of a *diacetate*, thus affording further proof of the above structure; a compound analysing as a *monoacetate* was also obtained. Both acetates were hydrolysed by acid to (IV), thus excluding the possibility of the monoacetate being a pyridone derivative (assuming that hydrolysis was not accompanied by a migration). Oxidation of the monoacetate and the diacetate gave the same compound, analysing as *ethyl* 4 : 6-*dihydroxy*-3-p-*nitrophenylsulphonyl*-2-*methylpyridine*-5-*carboxylate*, the

phenolic character being shown by its ready solubility in cold dilute sodium hydroxide and its insolubility in cold aqueous sodium bicarbonate. The loss of acetyl groups during oxidation is probably concerned with the presence of the " ethyl acetoacetate " grouping in the molecule. Attempts to reacetylate this sulphone-ester proved unsuccessful; either the acetylation did not proceed at all, or the sulphone was destroyed. Acid hydrolysis of the sulphone-ester gave 4 : 6-*dihydroxy*-3-p-*nitrophenylsulphonyl*-2-*methylpyridine*.

Reduction of both sulphones was most unsatisfactory; amorphous, dark-coloured products were obtained.

Roblin, Williams, and Anderson (*loc. cit.*) have shown that *p*-acetamidobenzenesulphinic acid (usually as its potassium salt) reacts readily with various reactive halogen compounds to give *p*-acetamidophenyl sulphones. We have shown that 4-chloropyridine (Wibaut and Brockman, *Rec. Trav. chim.*, 1939, **58**, 885) reacts smoothly with *p*-acetamido-, *p*-cyano-, and *p*-acetamidomethyl-benzenesulphinic acids and with *p*-toluenesulphinic acid (as neutral salts) to give 4-*p*-acetamido-(V), 4-p-*cyano*-(VI), and 4-p-*acetamidomethyl-phenylsulphonylpyridine* (VII) and 4-p-*tolylsulphonylpyridine*, respectively. Hydrolysis of (V) occurred readily (cf. *loc. cit.*), but we were not able to hydrolyse (VII) satisfactorily to the corresponding amino-compound (VIII). Oxidation of (V) with perbenzoic acid proceeded slowly and gave the N-*oxide* which was hydrolysed, but with more difficulty than (V), by acid to 4-p-*aminophenylsulphonylpyridine* N-*oxide*. Attempts to reduce (VI) by sodium and alcohol to 4-*p*-aminomethylphenylsulphonylpyridine [*i.e.*, (VIII)] were also unsuccessful.

Interaction of *p*-acetamidobenzenesulphinic acid and 4 : 6-dichloro-2-methylpyridine was also examined. With equimolecular amounts of the reagents, 6(or 4)-*chloro*-4(or 6)-p-*acetamidophenylsulphonyl*-2-*methylpyridine* was produced; this was hydrolysed satisfactorily to the *amino*-compound. With 2 mols. of the sulphinic acid, a mixture resulted, but a little 4 : 6-*bis*-p-*acetamidophenylsulphonyl*-2-*methylpyridine* was isolable; this could not be hydrolysed satisfactorily.

Experimental.

4-*Methylthiopyridine*.—Following the method of King and Ware (*loc. cit.*), 4-methylthiopyridine hydriodide was obtained in needles (from alcohol), m. p. 183°, and not 170° as reported by these authors (Found : C, 28·8; H, 3·1. Calc. for C_6H_8NIS : C, 28·4; H, 3·2%).

4-*Ethylthiopyridine Hydriodide*.—4-Thiopyridone (4·44 g.) was dissolved in boiling alcohol (50 c.c.), the solution cooled to 60°, and ethyl iodide (6·3 g.) in alcohol (10 c.c.) added. On cooling, the *hydriodide* separated (7·5 g.) After crystallisation from alcohol, this had m. p. 164—165° (Found : C, 32·0; H, 3·9. $C_7H_{10}NIS$ requires C, 31·5; H, 3·7%).

4-*Ethylsulphonylpyridine*.—The base, liberated from the foregoing hydriodide (7·5 g.) with sodium hydroxide solution, was extracted with ether, the ethereal solution dried (BaO), and the residual oil oxidised with a slight excess of 3% permanganate, the mixture being evaporated to dryness, care being taken not to overheat the residue. The latter was extracted with ether; on evaporation of the ether, an oil, which solidified on standing, was obtained. Crystallisation from ligroin–acetone gave the *compound* in white needles (1·8 g.), m. p. 29° (Found : C, 49·4; H, 5·7. $C_7H_9O_2NS$ requires C, 49·1; H, 5·3%).

Phenyl Octyl Sulphide.—Thiophenol (11·0 g.) was added to a solution of sodium (2·3 g.) in alcohol (50 c.c.) followed by a solution of *n*-octyl bromide (19·3 g.) in alcohol (25 c.c.). The solution was boiled for 1 hour, filtered from sodium bromide, and the product distilled; the *sulphide* had b. p. 175°/18 mm. (18·5 g.) (Found : C, 76·1; H, 10·1; S, 14·2. $C_{14}H_{22}S$ requires C, 75·7; H, 9·9; S, 14·4%). Oxidation of 8·2 g. with perhydrol (20 c.c.) in acetic acid (50 c.c.) at 100° for ¾ hour gave the *sulphone* (7·5 g.), b. p. 230°/19 mm. (Found : C, 66·1; H, 8·8; S, 12·5. $C_{14}H_{22}O_2S$ requires C, 66·15; H, 8·65; S, 12·6%).

p-*Nitrophenyl Octyl Sulphide*.—*n*-Octyl iodide (or the equivalent amount of bromide) (7·8 g.) and sodium *p*-nitrothiophenoxide (6·0 g.), were dissolved in alcohol (25 c.c.) and benzene (25 c.c.) and the solution was boiled for 3 hours. The solvent was evaporated, water added, and the product extracted with ether. The ethereal solution was dried (Na_2SO_4), the ether distilled, and the residue dissolved in ligroin (b. p. 40—60°), from which the *sulphide* separated in pale yellow prisms, m. p. 35° (3 g.) (Found : C, 63·1; H, 8·0; N, 5·5; S, 12·15. $C_{14}H_{21}O_2NS$ requires C, 62·9; H, 7·9; N, 5·24; S, 12·0%).

The sulphide (4 g.) in acetic acid (40 c.c.) was oxidised with perhydrol (9·0 c.c.) for 45 minutes at 100°. The *sulphone* was precipitated with water and crystallised from alcohol, forming yellow needles (4 g.), m. p. 52° (Found : C, 56·1; H, 7·1; N, 5·0; S, 10·8. $C_{14}H_{21}O_4NS$ requires C, 56·2; H, 7·0; N, 4·7; S, 10·7%).

p-*Aminophenyl Octyl Sulphone*.—The nitro-sulphone (5·2 g.), iron powder (15 g.), alcohol (100 c.c.), water (15 c.c.), and concentrated hydrochloric acid (1 c.c.) were heated, with stirring, under reflux for 3 hours. The mixture was made alkaline with ammonia, and the liquid filtered hot and evaporated to dryness. The residue was dissolved in boiling dilute hydrochloric acid (charcoal) and the amine liberated with sodium hydroxide. The *sulphone* (3·5 g.) formed needles, m. p. 105°, from alcohol (Found : C, 62·3; H, 8·5; N, 5·4; S, 12·0. $C_{14}H_{23}O_2NS$ requires C, 62·5; H, 8·55; N, 5·2; S, 11·9%).

Interaction of 4-*Chloropyridine and Sodium* p-*Nitrothiophenoxide*.—Sodium *p*-nitrothiophenoxide (3 g.) and 4-chloropyridine (2 g.) were dissolved in alcohol (60 c.c.) and boiled for 16 hours. The mixture was poured into water and the product collected. Crystallisation from alcohol gave pale yellow needles (1·1 g.) of 4 : 4′-dinitrodiphenyl sulphide, m. p. and mixed m. p. 156°.

Ethyl 4 : 6-*Dihydroxy*-3-p-*nitrophenylthio*-2-*methylpyridine*-5-*carboxylate.*—*p*-Nitrobenzenesulphenyl chloride (from 15·4 g. of pure 4 : 4′-dinitrodiphenyl disulphide) in dry chloroform (100 c.c.) was added to a solution of ethyl 4 : 6-dihydroxy-2-methylpyridine-5-carboxylate (19·7 g.) in warm nitrobenzene (200 c.c.) and the solution heated on the steam-bath for 20 hours during which time a solid slowly separated. The mixture was filtered whilst still hot, giving 12 g. of solid (*A*). On cooling, a further 8 g.(*B*) was obtained. Crystallisation of (*A*) from 2-methoxyethanol gave nearly colourless needles, m. p. 261° (decomp.) (Found : N, 8·0; S, 8·9), and of (*B*) needles, m. p. 256° (Found : C, 51·2; H, 4·2; N, 7·9; S, 8·9. $C_{15}H_{14}O_6N_2S$ requires C, 51·4; H, 4·0; H, 8·0; S, 9·1%), no depression in m. p. being observed on admixture of the two samples of the *ester*.

4 : 6-*Dihydroxy*-3-p-*nitrophenylthio*-2-*methylpyridine.*—The above ester (*A* or *B*) (2 g.) was boiled with concentrated hydrochloric acid (40 c.c.) and 2-methoxyethanol (30 c.c.) for 6 hours. On cooling, the *product* crystallised in minute needles (1·2 g.), m. p. 294° (decomp.) (Found : C, 51·6; H, 3·8; N, 9·8; S, 11·6. $C_{12}H_{10}O_4N_2S$ requires C, 51·8; H, 3·6; N, 10·1; S, 11·5%).

Ethyl 4 : 6-*Diacetoxy*-3-p-*nitrophenylthio*-2-*methylpyridine*-5-*carboxylate.*—The above ester (*B*) (10 g.) was heated on the steam-bath with fused sodium acetate (10 g.) and acetic anhydride (75 c.c.) for 4 hours. The reaction mixture was poured into water giving an oil, which solidified on being stirred. Crystallisation from alcohol gave the *diacetyl* derivative as fine needles (8·5 g.), m. p. 123° (Found : C, 52·6; H, 4·1; N, 6·5; S, 7·2. $C_{19}H_{18}O_8N_2S$ requires C, 52·5; H, 4·1; N, 6·5; S, 7·4%). Attempted acetylation with boiling acetic anhydride caused profound decomposition.

Ethyl 6(or 4)-*Hydroxy*-4(or 6)-*acetoxy*-3-p-*nitrophenylthio*-2-*methylpyridine*-5-*carboxylate.*—Acetylation of (*A*) under similar conditions to the above gave the *monoacetyl* derivative as nearly colourless needles (10 g.), m. p. 176° (Found : C, 51·7; H, 4·4; N, 7·3; S, 8·1. $C_{17}H_{16}O_7N_2S$ requires C, 52·0; H, 4·1; N, 7·1; S, 8·2%), soluble in cold dilute sodium hydroxide. Further acetylation could not be accomplished. Acetylation of (*A*) and (*B*) was carried out several times with the same results.

Ethyl 4 : 6-*Dihydroxy*-3-p-*nitrophenylsulphonyl*-2-*methylpyridine*-5-*carboxylate.*—The diacetate (8 g.) in glacial acetic acid (50 c.c.) and acetic anhydride (15 c.c.) was oxidised with perhydrol (8·5 c.c.) at 100° for ½ hour, during which time a solid slowly separated. The cooled reaction mixture was diluted with water, and the solid collected. After crystallisation from acetic acid, the *product* (5 g.) had m. p. 276° (decomp.) (Found : C, 47·1; H, 3·6; N, 7·3; S, 7·9. $C_{15}H_{14}O_8N_2S$ requires C, 47·1; H, 3·7; N, 7·3; S, 8·4%). Similar oxidation of the monoacetate gave the same product, m. p. and mixed m. p. 276°.

4 : 6-*Dihydroxy*-3-p-*nitrophenylsulphonyl*-2-*methylpyridine.*—The ester-sulphone (1·5 g.) was boiled with concentrated hydrochloric acid (30 c.c.) and 2-methoxyethanol (40 c.c.) for 6 hours. A white solid slowly separated, and was thrown out completely on cooling (1·1 g.). This *compound* had m. p. 303° (decomp.), and was completely insoluble in all the common solvents (Found : C, 47·3; H, 3·6; N, 9·0; S, 10·0. $C_{12}H_{10}O_8N_2S$ requires C, 46·5; H, 3·2; N, 9·0; S, 10·3%).

4-p-*Cyanophenylsulphonylpyridine.*—Sodium *p*-cyanobenzenesulphinate (27·5 g.) in water (250 c.c.) was added to a solution of 4-chloropyridine (16·2 g.) in alcohol (50 c.c.). Traces of copper powder and iodine were added, and the solution was boiled for 3½ hours. The *sulphone* separated on cooling (26·5 g.), and, after crystallisation from alcohol, formed pale yellow needles, m. p. 182° (Found : N, 11·1; S, 13·0. $C_{12}H_8O_2N_2S$ requires N, 11·5, S, 13·1%).

4-p-*Tolylsulphonylpyridine.*—4-Chloropyridine (3 g.) in alcohol (25 c.c.) was added to a solution of *p*-toluenesulphinic acid (4·1 g.) and potassium hydroxide (1·5 g.) in water (50 c.c.). Traces of copper powder and iodine were added, and the solution was refluxed for 1½ hours. On cooling, the *sulphone* separated and, after crystallisation from alcohol, formed colourless needles (4·5 g.), m. p. 137—138° (Found : C, 61·4; H, 4·7. $C_{12}H_{11}O_2NS$ requires C, 61·8; H, 4·7%).

p-*Acetamidomethylbenzenesulphinic Acid.*—*p*-Acetamidomethylbenzenesulphonyl chloride (Bergeim and Braker, *J. Amer. Chem. Soc.*, 1944, **66**, 1459) (29 g.) was shaken for 2 hours with a solution of sodium sulphite ($Na_2SO_3,7H_2O$) (60 g.) in water (120 c.c.) with frequent addition of 50% sodium hydroxide solution to keep the mixture slightly alkaline. The solution was filtered and acidified with sulphuric acid. The product was collected, and, after crystallisation from a small volume of water, formed white needles (10 g.), m. p. 138—139° (decomp.).

4-p-*Acetamidomethylphenylsulphonylpyridine.*—A solution of the above sulphinic acid (10·65 g.) and potassium hydroxide (2·8 g.) in water (50 c.c.) was added to a solution of 4-chloropyridine (5·7 g.) in alcohol (10 c.c.). Traces of copper powder and iodine were added, and the solution was boiled for 20 minutes. The *sulphone* separated on cooling, and, after crystallisation from water, formed minute needle-shaped crystals (9·3 g.), m. p. 170—171° (Found : N, 9·4; S, 10·8. $C_{14}H_{14}O_3N_2S$ requires N, 9·7; S, 11·0%).

4-p-*Aminophenylsulphonylpyridine* N-*Oxide.*—4-*p*-Acetamidophenylsulphonylpyridine (5·52 g.) dissolved in chloroform (530 c.c.) was added to 70 c.c. of a chloroform solution of perbenzoic acid containing 0·4 g. of active oxygen. The solution was kept for two weeks in the refrigerator (unreacted perbenzoic acid being determined iodometrically at frequent intervals). The chloroform solution was evaporated to one third of its volume and shaken with excess of sodium carbonate solution; a colourless solid then separated. This was collected, and on crystallising from alcohol formed small agglomerations of flattened needles (3·6 g.), m. p. 242—243° (Found : C, 53·9; H, 4·2; N, 10·4; S, 10·9. $C_{13}H_{12}O_4N_2S$ requires C, 53·4; H, 4·1; N, 9·6; S, 10·9%). The *acetamido-sulphone oxide* was hydrolysed by boiling with concentrated hydrochloric acid (50 c.c.) and water (10 c.c.) for 6 hours; the *product* after crystallisation from alcohol, had m. p. 244—245° (decomp.) (Found : N, 11·5; S, 13·2. $C_{11}H_{10}O_3N_2S$ requires N, 11·2; S, 12·8%), depressed to 209—210° on admixture with the acetyl derivative.

6(or 4)-*Chloro*-4(or 6)-p-*aminophenylsulphonyl*-2-*methylpyridine.*—4 : 6-Dichloro-2-methylpyridine (Collie *et al.*, *J.*, 1892, 725; 1895, 408) (5·1 g.) in alcohol (100 c.c.) was added to a solution of acetamidobenzenesulphinic acid (6·3 g.) and potassium hydroxide (1·75 g.) in water (250 c.c.). Traces of copper powder and iodine were added, and the solution was boiled for 15 hours. The solution was cooled, and the solid (10 g.) collected. Crystallisation from aqueous 2-methoxyethanol gave the *compound* as lustrous, white needles, m. p. 250—252° (Found : C, 52·5; H, 4·6; N, 8·9; S, 10·1.

$C_{14}H_{13}O_3N_2ClS$ requires C, 51·8; H, 4·0; N, 8·6; S, 9·9%). Hydrolysis with 6N-hydrochloric acid gave the *amino-sulphone* which, crystallised from alcohol, had m. p. 172° (Found: C, 51·3; H, 3·9; N, 10·2; S, 11·1. $C_{12}H_{11}O_2N_2ClS$ requires C, 51·0; H, 3·9; N, 9·9; S, 11·3%).

4 : 6-*Bis*-p-*acetamidophenylsulphonyl*-2-*methylpyridine*.—*p*-Acetamidobenzenesulphinic acid (12·5 g.), and potassium hydroxide (3·53 g.) were dissolved in water (150 c.c.) and added to a solution of 4 : 6-dichloro-2-methylpyridine (3 g.) in alcohol (75 c.c.). Traces of copper powder and iodine were added, and the solution was boiled for 20 hours. The alcohol was evaporated, and on cooling a white solid separated. After three crystallisations from 2-methoxyethanol the *compound* formed lustrous, hair-like, white needles, m. p. 275—276°, unchanged by further crystallisation (Found: C, 53·5; H, 4·9; S, 13·1. $C_{22}H_{21}O_6N_3S_2$ requires C, 54·2; H, 4·3; S, 13·1%).

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11. *Synthetic Mydriatics.*

By A. H. FORD-MOORE and H. R. ING.

The preparation of some forty alkamine esters, mostly of benzilic acid, is described and the results of their testing as mydriatics are discussed.

SINCE the extensive study of synthetic tropeines by Jowett and Pyman (*7th Internat. Cong. Appl. Chem.*, 1909, IV*A*, 1, 335) and the work of von Braun, Braunsdorf, and Räth (*Ber.*, 1922, **55**, 1666) on the tropic esters of simple alkamines, little work has been published on synthetic mydriatics of the atropine type until recently, although a good deal of work has been done in France and U.S.A. on synthetic spasmolytics. Spasmolytic properties, however, appear to be less highly specific than mydriatic properties and more closely allied to local anæsthetic properties.

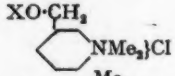
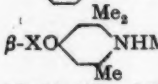
In 1942 Blicke and Maxwell (*J. Amer. Chem. Soc.*, 1942, **64**, 428, 431) reported that the benzilic esters of diethylamino- and piperidino-ethanols and their methobromides were excellent mydriatics when tested on the rabbit's eye in 1—2% solutions, but no quantitative comparison with atropine was made. Later Blicke and Kaplan (*ibid.*, 1943, **65**, 1967) found that the benzilic esters of simple alkamines were usually more potent mydriatics than the corresponding esters of mandelic acid or of any of the four isomeric phenylhydroxypropionic acids, including tropic acid.

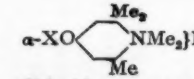
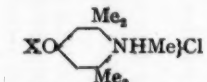
The mydriatic action of atropine is due to the drug antagonising acetylcholine released at the terminations of the parasympathetic (cholinergic) nerves to the circular muscle of the iris; stimulation of these nerves constricts the pupil and atropine prevents this effect. It occurred to us that acetylcholine might be antagonised by a suitable choline ester, and in fact both *tropylcholine chloride* and *benzilylcholine chloride* were found to have mydriatic properties, the latter being about a third as active as atropine in the mouse and about twice as active as the former. At the time (1942) these were the only mydriatic choline esters known to us, but Swan and White (*Proc. Soc. Exp. Biol. Med.*, 1943, **53**, 164) announced the discovery of mydriatic dialkylcarbamic esters of choline of which di-*n*-butylcarbamylcholine was the best. Recently Loew, Kaiser, and Anderson (*Fed. Proc.*, 1946, **5**, 190) have reported that the diphenylmethyl ether of choline has mydriatic properties.

Starting from benzilylcholine a search was made for more active benzilic esters of the same type. All our compounds were tested for mydriatic potency by Dr. Edith Bülbring and Mrs. Izabella Wajda in the Department of Pharmacology, Oxford, by comparing the effects of the synthetic substances and of atropine in groups of mice by direct measurement of the size of the pupil (Ing, Dawes, and Wajda, *J. Pharmacol.*, 1945, **85**, 85; cf. Pulewka, *Arch. exp. Path. Pharm.*, 1932, **168**, 307). Later Mr. G. S. Dawes compared the effects of the synthetic mydriatics and of atropine on the salivary secretion and blood pressure of the cat; his results are incorporated in the paper by Ing, Dawes, and Wajda (*loc. cit.*).

The synthetic benzilic esters are listed in Table I, together with their serial numbers and their relative molar potencies in terms of atropine sulphate = 100; the potencies of the more active compounds are also given on a dose–weight basis in parentheses. Molar potencies are more illuminating for studies on the structure and action of drugs, but for clinical purposes the relative potencies of equal doses are usually more useful; thus although E27 is intrinsically more active than E3, it presents no advantage over an equal dose of E3 because of its higher molecular weight. Atropine, E3, and E27 all have approximately the same activity in equal doses in mice,

TABLE I.

No.	Benzilic ester [X = $CPh_2(OH)\cdot CO$].	Potency.	Method of synthesis.	Crystallised from:	M. p.	Formula.	Found (%). C.	Found (%). H.	Required (%). C.	Required (%). H.	Notes.
C4	$CH_2(OX)\cdot CH_2\cdot NHMe_2\}Cl$	12·6	*a*	Ethanol or water	188—189°	$C_{18}H_{22}O_3NCl$	64·1	6·6	64·4	6·6	1
C1	$CH_2(OX)\cdot CH_2\cdot NMe_3\}Cl,\frac{1}{2}H_2O$	31	*b*	Ethanol–acetone	218	$C_{19}H_{24}O_3NCl,\frac{1}{2}H_2O$	63·6	7·1	63·6	7·0	2
E3	$CH_2(OX)\cdot CH_2\cdot NMe_2Et\}Cl$	104·4 (100)	*b*, *c*	,,	213	$C_{20}H_{26}O_3NCl$	66·1	7·2	66·0	7·2	3
E4	$CH_2(OX)\cdot CH_2\cdot NMe_2Pr^{\beta}\}Cl$	92·5 (85)	*b*	,,	199—200	$C_{21}H_{28}O_3NCl$	67·0	7·5	66·8	7·4	
E5	$CH_2(OX)\cdot CH_2\cdot NMe_2Pr^{\alpha}\}Br$	22	*c*	Ethanol–ethyl acetate	186—187	$C_{21}H_{28}O_3NBr$	59·9	6·5	59·7	6·6	
E6	$CH_2(OX)\cdot CH_2\cdot NMe_2\cdot C_3H_5\}Br$	28	*c*	Acetone	161—162	$C_{21}H_{26}O_3NBr$	60·2	6·3	60·0	6·2	
E7	$CH_2(OX)\cdot CH_2\cdot NMe_2Bu\}Br$	10·5	*c*	Ethanol–acetone	143—144	$C_{22}H_{30}O_3NBr$	60·0	7·1	60·5	6·9	
E11	$CH_2(OX)\cdot CH_2\cdot NMe_2Am\}Br$	13	*c*	Acetone	129—130	$C_{23}H_{32}O_3NBr$	61·4	7·2	61·3	7·2	
E25	$CH_2(OX)\cdot CH_2\cdot NMe_2\cdot CH_2\cdot CH_2Br\}Br$	30	*c*	Ethanol–acetone	173	$C_{20}H_{25}O_3NBr_2$	49·5	5·1	49·3	5·2	
E1	$CH_2(OX)\cdot CH_2\cdot NHEt_2\}Cl$	6·3	*a*	Ethanol–acetone	174—175	$C_{20}H_{26}O_3NCl$	—	—	—	—	4
E2	$CH_2(OX)\cdot CH_2\cdot NEt_2Me\}Cl$	64	*b*	,,	184—185	$C_{21}H_{28}O_3NCl$	66·6	7·4	66·6	7·5	5
E14	$CH_2(OX)\cdot CH_2\cdot NEt_3\}Br$	83 (66)	*c*	,,	220	$C_{23}H_{30}O_3NBr$	60·3	6·5	60·5	6·9	6
E15	$CH_2(OX)\cdot CH_2\cdot NEt_2Pr^{\alpha}\}Br$	22	*c*	,,	171	$C_{23}H_{32}O_3NBr$	61·6	7·1	61·3	7·2	
E16	$CH_2(OX)\cdot CH_2\cdot NHPr^{\beta}_2\}Cl$	9	*a*	Methyl ethyl ketone	147—148	$C_{22}H_{30}O_3NCl$	67·5	7·7	67·4	7·7	
E17	$CH_2(OX)\cdot CH_2\cdot NMePr^{\beta}_2\}I$	57·3	*c*	Ethanol or water	174—175	$C_{23}H_{32}O_3NI$	55·6	6·2	55·5	6·4	
E9	$CH_2(OX)\cdot CH_2\cdot NMeEtPr^{\alpha}\}Br$	27·6	*c*	Ethanol–acetone	189	$C_{22}H_{30}O_3NBr$	59·9	6·8	60·5	6·9	
E8	$CH_2(OX)\cdot CH_2\cdot CH_2\cdot NEt_2Me\}Cl$	60	*b*	,,	195	$C_{22}H_{30}O_3NCl$	67·6	7·6	67·4	7·7	
E10	$CH_2(OX)\cdot CH_2\cdot CH_2\cdot NEtMe_2\}Cl$	64	*b*	,,	181	$C_{21}H_{28}O_3NCl$	66·3	7·5	66·6	7·5	
E12	$CHMe(OX)\cdot CH_2\cdot NMe_2Et\}Br$	9·7	*c*	Ethanol	213	$C_{21}H_{28}O_3NBr$	60·0	6·5	59·7	6·6	
E26	$CHMe(OX)\cdot CMe_2\cdot CH_2\cdot NMe_2H\}Cl$	0	*d* (130°)	Methyl ethyl ketone	174—175	$C_{22}H_{30}O_3NCl$	66·6	7·7	67·4	7·9	
E27	$CH_2(OX)\cdot CMe_2\cdot CH_2\cdot NMe_2Et\}I$	142 (99)	*c*	Methyl acetate	136—137	$C_{23}H_{32}O_3NI$	55·6	6·5	55·3	6·5	
P1	$CH_2(OX)\cdot CH_2\cdot NH\cdot C_5H_{10}\}Cl$	0·6	*a*	Ethanol or acetone	170—171	$C_{21}H_{26}O_3NCl$	67·7	6·9	67·2	6·9	4, 4a
P2	$CH_2(OX)\cdot CH_2\cdot NMe\cdot C_5H_{10}\}Cl$	17·3	*b*	Ethanol–acetone	215	$C_{22}H_{28}O_3NCl$	67·8	7·2	67·9	7·3	5
P6	$CHMe(OX)\cdot CH_2\cdot NH\cdot C_5H_{10}\}Cl$	0	*a*	Ethanol–ether	167—168	$C_{22}H_{28}O_3NCl$	—	—	—	—	4
M1	$CH_2(OX)\cdot CH_2\cdot NH\cdot C_4H_8O\}Cl$	0	*a*	Ethanol–ethyl acetate	181	$C_{20}H_{24}O_4NCl$	—	—	—	—	4
M2	$CH_2(OX)\cdot CH_2\cdot NMe\cdot C_4H_8O\}Cl$	4·5	*b*	Ethanol	207—208	$C_{21}H_{26}O_4NCl$	64·1	6·7	64·3	6·7	5
M6	$CH_2(OX)\cdot CH_2\cdot NMe\cdot C_4H_8S\}Cl$	14	*b*	Ethanol–acetone	227 (decomp.)	$C_{21}H_{26}O_3NClS$	61·8	6·5	61·8	6·6	
M7	$CH_2(OX)\cdot CH_2\cdot NMe\cdot C_4H_8SO_2\}Cl$	0	*b*	Ethanol	225 (decomp.)	$C_{21}H_{26}O_5NClS$	56·7	6·0	56·3	5·9	7
P7		65	*b*	Ethanol–acetone	238 (decomp.)	$C_{22}H_{28}O_3NCl$	67·5	7·0	67·8	7·2	
P8		16	*d* (160°)	Ethanol	244 (decomp.)	$C_{23}H_{30}O_3NCl$	68·2	7·5	68·4	7·4	
P9	Methiodide of P8	170 (116)	*c*	Ethanol or water	225 (decomp.)	$C_{24}H_{32}O_3NI$	—	—	—	—	8
P10	Methochloride of P8 + C_3H_6O	165 (120)	*c*	*iso*Propanol	224 (decomp.)	$C_{24}H_{32}O_3NCl,C_3H_6O$	67·7	8·3	67·8	8·4	9
P11											

P11		196 ?		*c*	Water	239 (decomp.)	$C_{24}H_{32}O_3NI$	56·8	6·3	56·6	6·3	
P12	Chloride, corresponding to P11	143	(104)	*c*	*iso*Propanol	212 (decomp.)	$C_{24}H_{32}O_3NCl,C_3H_8O$	67·4	8·5	67·8	8·4	10
P13		0		*d* (140°)	Ethanol–acetone	253 (decomp.)	$C_{24}H_{32}O_3NCl$	68·8	7·7	69·0	7·7	
P14	Ethobromide of P13	0		*c*	Ethanol	255 (decomp.)	$C_{26}H_{36}O_3NBr$	63·0	7·3	63·5	7·6	

The methods of synthesis (column 4) are listed in the experimental section. Potencies (column 3) are relative molar potencies (atropine sulphate = 100) on the eye of the mouse; the figures in parentheses are potencies on a dose–weight basis (atropine sulphate = 100).

1. Previously made by Blicke and Kaplan (*loc. cit.*) who record m. p. 183—185°.
2. Found (anhydrous): C, 65·1; H, 6·9. $C_{19}H_{24}O_3NCl$ requires C, 65·2; H, 6·9%.
3. Method *b* gives 75% yield; method *c*: dimethylaminoethyl benzilate heated with excess of ethyl chloride in acetone at 100° for 8—12 hours; the product crystallized from the reaction mixture, any unchanged tertiary base being recovered from the mother liquor.
4. Previously made by Blicke and Maxwell (*loc. cit.*); (4a) who record m. p. 175—176°.
5. Corresponding bromide made by Blicke and Maxwell.
6. The *chloride*, m. p. 235°, is more soluble in water, less soluble in alcohol, and has the same potency (Found: C, 67·4; H, 7·8. $C_{22}H_{30}O_3NCl$ requires C, 67·4; H, 7·7%).
7. M7 could not be obtained by oxidising M6 with hydrogen peroxide; β-chloroethylthiomorpholine dioxide was obtained from divinyl sulphone and ethanolamine, followed by thionyl chloride, and was converted into its methiodide.
8. Sparingly soluble in water (Found: I, 25·0. $C_{24}H_{32}O_3NI$ requires I, 24·9%).
9. Soluble in water; *iso*propanol of crystallization not lost at 100° in a vacuum (Found: Cl, 7·6. $C_{24}H_{32}O_3NCl$ requires Cl, 7·4%).
10. Began to lose *iso*propanol of crystallization at 150°, effervesced at 159°, resolidified, and finally melted at 212° (decomp.).

TABLE II.

No.	Compound.	Potency.	Method of synthesis.	Crystallized from:	M. p.	Formula.	Found (%). C.	Found (%). H.	Required (%). C.	Required (%). H.
C2	$CMePh(OH)\cdot CO_2\cdot CH_2\cdot CH_2\cdot NMe_3\}Cl,H_2O$	0	*b*	Ethanol–acetone	170° *	$C_{14}H_{22}O_3NCl,H_2O$	54·7	8·1	54·9	7·9
C3	$CHPh(CH_2\cdot OH)\cdot CO_2\cdot CH_2\cdot CH_2\cdot NMe_3\}Cl,\frac{1}{2}H_2O$	12·5	*b*	Methanol–ethyl acetate	178—179	$C_{14}H_{22}O_3NCl,\frac{1}{2}H_2O$	56·9	7·6	56·7	7·7
P3	$CMePh(OH)\cdot CO_2\cdot CH_2\cdot CH_2\cdot NMe\cdot C_5H_{10}\}Cl$	0	*b*	Ethanol–acetone	164—165	$C_{17}H_{26}O_3NCl$	61·8	8·2	62·3	7·9
M3	$CHPh(CH_2Cl)\cdot CO_2\cdot CH_2\cdot CH_2\cdot NH\cdot C_4H_8O\}Cl$	0	*d*	,,	149	$C_{15}H_{21}O_3NCl_2$	54·3	6·5	53·9	6·3
M4	$C_6H_4<C_6H_4>C(OH)\cdot CO_2\cdot CH_2\cdot CH_2\cdot NH\cdot C_4H_8O\}Cl$	0	*a*	Ethanol	195—196	$C_{20}H_{22}O_4NCl$	64·0	6·2	64·1	5·9
M5	$CMePh(OH)\cdot CO_2\cdot CH_2\cdot CH_2\cdot NH\cdot C_4H_8O\}Cl$	0	*a*	,,	192 (decomp.)	$C_{16}H_{24}O_4NCl$	58·1	7·4	58·3	7·3
E13	$CPh_2(OH)\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot NMe_2Et\}Br$	11	*c*	Ethanol–acetone	227	$C_{20}H_{27}O_2N_2Br$	58·8	6·6	59·0	6·7
E21	$CPhC_{10}H_7\beta(OH)\cdot CO_2\cdot CH_2\cdot CH_2\cdot NMe_2Et\}Cl$	0	*b*	,,	221 (decomp.)	$C_{24}H_{28}O_3NCl$	69·6	6·7	69·7	6·8
E22	$CPhC_{10}H_7\alpha(OH)\cdot CO_2\cdot CH_2\cdot CH_2\cdot NMe_2Et\}Cl$	5	*b*	Ethanol–ethyl acetate	194—195	$C_{24}H_{28}O_3NCl$	69·5	6·8	69·7	6·8

* Began to lose water at 163°.

but E3 has the advantage over E27 that it can be prepared from more readily accessible materials.

The mydriatic effect of E3 in the mouse, the cat, and man is more transient than that of atropine and is, in this respect, more comparable with that of homatropine; E3 also produces paralysis of accommodation in man.

In the homologous series $CH_2(OX)\cdot CH_2\cdot NMe_2R\}Hal$. [X = $CPh_2(OH)\cdot CO$ and R = an alkyl group], a sharp maximum in mydriatic activity occurs when R = Et, and it is interesting to note that the most active mydriatic discovered by Swan and White (*Amer. J. Ophthal.*, 1944, **27**, 933) was the dibutylcarbamic ester of the same alkamine (X = $NBu_2\cdot CO$; R = Et). The relatively high activity of E4 (R = Pr^{β}) is abruptly diminished by the introduction of a second *iso*propyl group (E17); the *n*-propyl group (E5) is less effective than the *iso*propyl group. In the series $CH_2(OX)\cdot CH_2\cdot NEt_2R\}Hal$. the maximum again occurs when R = Et.

The propanolamine derivatives E8 and E10 were both less active and less toxic than their ethanolamine analogues. The introduction of a β-methyl group into E3, as in E12, leads to a sharp drop in activity, a result which recalls the decline in cholinergic preperties in passing from acetylcholine to acetyl-β-methylcholine. The high activity of E27 is interesting because Fromherz (*Arch. exp. Path. Pharm.*, 1933, **173**, 116) examined an analogous compound $CH_2(OX)\cdot CMe_2\cdot CH_2\cdot NEt_2Me\}SO_4Me$, which produced mydriasis in cats in 0·1% solution (atropine, 0·001%; *loc. cit.*, p. 126); the tertiary base hydrochloride, $CH_2(OX)\cdot CMe_2\cdot CH_2\cdot NEt_2H\}Cl$, was about half as active, and the tropic ester of the tertiary base was scarcely mydriatic at all.

The piperidinoethanol compounds P1 and P2, which Blicke and Maxwell classed as " excellent " mydriatics, proved to be relatively feeble and much less active than E2, which these authors examined as the bromide and also classified as " excellent ". The morpholino- and thiomorpholino-compounds (M1, M2, M6, and M7) were even more feeble in their action.

Fromherz (*loc. cit.*) and Blicke and Kaplan (*loc. cit.*) noted that benzilic esters of alkamines were better mydriatics than the corresponding tropic esters, and we have already noted a similar result for benzilyl- and tropyl-choline; an even more striking example of the efficacy of benzilic acid in mydriatic esters is provided by the compounds P8 to P10. Eucatropine is the mandelic ester of the β-isomeride of 4-hydroxy-1 : 2 : 2 : 6-tetramethylpiperidine, and P8 is the corresponding *benzilic* ester; in the mouse eucatropine hydrochloride has a molar potency of 0·4 whereas that of P8 is 16; eucatropine methiodide has a potency of 2·8, and the *metho*-salts of P8 have 165—170. The α-isomeride of 4-hydroxy-1 : 2 : 2 : 6-tetramethylpiperidine also yields a mydriatic benzilic ester, the *methochloride* (P12), having a molar potency of 143; the *methiodide* (P11) was sparingly soluble in water, and too few mice were used for the figure in Table I to be reliable. The benzilic ester of the symmetrical 4-hydroxy-1 : 2 : 2 : 6 : 6-pentamethylpiperidine (P13) was inactive.

Although P10 is more potent than E3 in the mouse, its mydriatic effect is also more transient; in man it proved to be a very weak mydriatic and uncertain in action; like eucatropine it is not a cycloplegic drug (personal communication by Professor Ida Mann).

One of the most striking results of a study of the benzilic esters listed in Table I is that the salts of tertiary bases are much less active than their metho-salts; thus the compounds C4, E1, E16, P1, M1, and P8 are markedly less active than their respective metho-salts C1, E2, E17, P2, M2, and P10. Fromherz (*loc. cit.*) and Blicke and Maxwell (*loc. cit.*) noted a similar effect, and the point has been fully discussed by Ing, Dawes, and Wajda (*loc. cit.*).

Mydriatic activity appears to be more specifically associated with the nature of the acyl group than with that of the alkamine; this is illustrated by the results listed in Table II. Several α-hydroxy-α-phenylpropionic esters (C2, P3, M5) had no activity although the benzilic analogues C1 and P2 were active. Replacement of the benzilic ester group in E3 by the benzilamido-group (E13) reduced the activity to a tenth.

An attempt to find an asymmetric analogue of E3 in order to discover whether compounds of this type display any stereochemical specificity comparable with that of the belladonna alkaloids was unsuccessful; the *phenyl-β-naphthylglycollic* ester was inactive and the *phenyl-α-naphthylglycollic* ester only feebly active.

These results on modifications of the benzilyl group are in striking contrast with those which have been obtained by numerous authors on spasmolytic alkamine esters in which the nature of the acyl group can be varied widely without drastic loss of activity.

The preparation of the alkamine esters presented no special difficulty. The method of Horenstein and Pählicke (*Ber.*, 1938, **71**, 1654)—*i.e.*, by heating the chloroalkylamine salt of an organic acid—proceeded very easily when the N atom was quaternary, but required higher

temperatures when the N atom was tertiary or the Cl atom attached to a secondary carbon. The benzilic esters of 4-hydroxy-1 : 2 : 2 : 6-tetramethylpiperidines were prepared by heating the dry hydrochlorides of the latter with diphenylchloroacetyl chloride, a method which we owe to Dr. F. E. King; the α-chlorine atom of the product is readily hydrolysed in aqueous solution. A similar method was used to prepare the ββ-dimethylpropanolamine derivatives E26 and E27.

E3 has been used in the Oxford Eye Hospital and elsewhere during the last two years with some success. Clinical reports on its use have been published by Mann (*Brit. J. Ophthal.*, 1946, **30**, 8) and by Riddell (*ibid.*, p. 1). It is proposed to give E3 the name Lachesine (from Λαχεσις, one of the Fates, whose sister Ἀτροπος gave her name to atropine).

Experimental.

[Analyses (all micro-) are by Weiler and Strauss. Melting points are uncorrected.]

Benzilic Esters.—The methods of preparation are indicated by letters *a*, *b*, *c*, and *d* in Table I.

(*a*) An intimate mixture of the chloroalkyldialkylamine hydrochloride and potassium benzilate was heated at 140—160° for 3—4 hours and the cooled melt extracted with hot ethanol. The alcohol extract was evaporated and the product stirred with acetone and separated. In a few cases the chloroalkylamine and benzilic acid were heated in boiling chlorobenzene, from which the benzilic ester hydrochloride separated.

(*b*) The chloroalkyltrialkylammonium chloride (or iodide) was heated in boiling ethanol with potassium (or silver) benzilate for 1 hour. The solution was filtered from metal halide, evaporated, and the residue heated at 100° until it solidified completely; it was stirred with acetone, collected, and recrystallised.

Methods *a* and *b* yield homogeneous products; any chloroalkylammonium benzilate which has failed to undergo the Horenstein and Pählicke rearrangement remains in the acetone used to wash the product.

(*c*) The tertiary aminoalkyl benzilate was heated with an alkyl halide without a solvent or in acetone. Methochlorides were usually obtained by digesting the methiodide with silver chloride in methanol.

(*d*) The dry tertiary amino-alcohol hydrochloride (prepared in ethanol but not usually isolated) was heated with diphenylchloroacetyl chloride at the temperature indicated in parentheses until the evolution of hydrogen chloride ceased (3—5 hours). The melt was dissolved in hot water, cooled, diluted, and the ester precipitated by the addition of dilute ammonia solution.

Miscellaneous Esters.—These (Table II) were prepared by analogous methods; *i.e.*, (*a*) from the chloroalkylamine hydrochloride and the potassium salt of the acid; (*b*) from the chloroalkyltrialkylammonium halide and the potassium (or silver) salt of the acid in ethanol; (*c*) from the tertiary base and the alkyl halide; (*d*) from the amino-alcohol and the acid chloride.

The Basic Moieties.—Tertiary chloroalkylamine hydrochlorides were prepared by the method used by Gough and King (*J.*, 1928, 2436) for diethylchloroethylamine hydrochloride. Quaternary chloroalkylammonium chlorides were prepared (i) by addition of methyl iodide to the tertiary base and subsequent digestion of the product with silver chloride, or (ii) by keeping the quaternary hydroxyalkylammonium chloride with a chloroform solution of thionyl chloride for several hours and evaporating the clear solution so obtained. The following compounds were prepared: trimethyl-β-chloroethylammonium chloride, prisms from ethanol, m. p. 241° (Found: C, 38·1; H, 8·4. Calc. for $C_5H_{13}NCl_2$: C, 38·0; H, 8·2%); dimethyl-β-chloroethylamine hydrochloride (Slotta and Behnisch, *Ber.*, 1935, **68**, 754); *dimethylethyl-β-hydroxyethylammonium picrate*, yellow needles, m. p. 251° (Found: C, 41·5; H, 5·27. $C_{13}H_{18}O_8N_4$ requires C, 41·6; H, 5·24%); *dimethylethyl-β-chloroethylammonium chloride*, hygroscopic prisms from ethanol–acetone, m. p. 231° (decomp.) (Found: C, 41·85; H, 8·85. $C_6H_{15}NCl_2$ requires C, 41·86; H, 8·72%); *picrate*, orange needles from methanol, m. p. 200° (Found: C, 39·3; H, 4·7. $C_{12}H_{17}O_7N_4Cl$ requires C, 39·5; H, 4·7%); *dimethyl-β-hydroxyethylisopropylammonium chloride*, hygroscopic prisms from *iso*butanol (Found: C, 49·8; H, 10·8. $C_7H_{18}ONCl$ requires C, 50·1; H, 10·7%); *β-chloroethylisopropylamine hydrochloride*, fine needles from acetone or methyl ethyl ketone, m. p. 180—181° (Found: C, 38·1; H, 8·25. $C_5H_{13}NCl_2$ requires C, 38·0; H, 8·23%); *β-chloroethyldiisopropylamine hydrochloride*, diamond-shaped prisms from acetone, m. p. 110° (Found: C, 47·9; H, 9·5. $C_9H_{19}NCl_2$ requires C, 48·0; H, 9·5%); *dimethyl-β-chloropropylamine hydrochloride*, hygroscopic needles m. p. 196° (Found: C, 37·9; H, 8·3. $C_5H_{13}NCl_2$ requires C, 38·0; H, 8·2%); *methyl dimethylamino-tert.-butyl ketone hydrobromide*, less hygroscopic than the hydrochloride, m. p. 174° (decomp.) (Found: C, 43·0; H, 8·1. $C_8H_{18}ONBr$ requires C, 42·9; H, 8·1%); *picrate*, yellow needles from methanol, m. p. 150° (Found: C, 45·6; H, 5·5. $C_{14}H_{20}O_8N_4$ requires C, 45·2; H, 5·4%); *3-chloro-1-dimethylamino-2 : 2-dimethyl-n-butane picrate*, from ethanol, m. p. 160° (Found: C, 43·3; H, 5·4. $C_{14}H_{21}O_7N_4Cl$ requires C, 42·8; H, 5·4%); *3-dimethylamino-2 : 2-dimethylpropanol hydrobromide*, obtained by reduction of the corresponding aldehyde (Mannich, Lesser, and Silten, *Ber.*, 1932, **65**, 381) by means of aluminium *iso*propoxide, formed plates from *iso*propanol, m. p. 158—159° (Found: C, 40·4; H, 8·3. $C_7H_{19}ONBr$ requires C, 39·6; H, 8·5%); β-chloroethylpiperidine (Dunlop, *J.*, 1912, **101**, 2002) gave a *methiodide*, m. p. 176—177°, from ethanol (Found: N, 4·6. $C_8H_{17}NClI$ requires N, 4·8%); piperidine-3-carbinol (Sandborn and Marvel, *J. Amer. Chem. Soc.*, 1928, **50**, 565) was methylated with formic acid and formalin and the product treated with thionyl chloride followed by methyl iodide to give 1 : 1-*dimethyl-3-chloromethylpiperidinium iodide*, which crystallised from ethanol in prisms, m. p. 176—177° (Found: C, 33·4; H, 5·5. $C_8H_{17}NClI$ requires C, 33·2; H, 5·8%).

Reduction of vinyldiacetonamine (21 g.) by means of aluminium *iso*propoxide and crystallisation of the product from benzene gave the β-alkamine (17 g.), m. p. 159—161°, and from the mother liquor a mixture (m. p. 120—123°; 3·5 g.) of the α- and β-alkamines. The β-alkamine was methylated with

formalin and formic acid and the *N*-methyl-β-alkamine purified by sublimation in a vacuum; m. p. 77—78° (Harries, *Annalen*, 1897, **294**, 352, records m. p. 70—72°). The β-alkamine (5 g.), boiled in amyl alcohol (100 c.c.) containing sodium (10 g.) for 30 hours, gave the α-form (3·6 g.), m. p. 137—138°. ***N*-β-*Hydroxyethylthiomorpholine methochloride***, from *N*-methylthiomorpholine and ethylene chlorohydrin, crystallised from ethanol, m. p. 258° (decomp.) (Found: C, 42·4; H, 8·3. $C_7H_{16}ONClS$ requires C, 42·3; H, 8·2%); ***N*-β-*chloroethylthiomorpholine methochloride*** crystallised from ethanol–acetone and decomposed at 232—235° without melting (Found: C, 38·6; H, 6·9. $C_7H_{15}NCl_2S$ requires C, 38·9; H, 7·0%).

β-Dimethylaminoethylamine formed a ***monobenzilate***, m. p. 152°, from ethanol (Found: C, 68·7; H, 7·6. $C_{16}H_{24}O_3N_2$ requires C, 68·3; H, 7·6%) and a ***dibenzilate***, m. p. 168—169°, from ethanol (Found: C, 70·3; H, 6·67. $C_{30}H_{36}O_4N_2$ requires C, 70·5; H, 6·65%). The former was heated at 185° for 2 hours and a further ½ hour in a vacuum to remove volatile products; the product was extracted with benzene, from which ***dimethylaminoethyl benzilamide hydrogen benzilate*** separated; m. p. 126°, from chloroform–light petroleum (Found: C, 72·3; H, 6·4; N, 5·1. $C_{30}H_{34}O_5N_2$ requires C, 73·0; H, 6·5; N, 5·3%). The free ***amide*** crystallised from benzene–light petroleum, m. p. 124° (Found: C, 72·5; H, 7·4. $C_{16}H_{22}O_2N_2$ requires C, 72·5; H, 7·4%), and gave E 13 with ethyl bromide.

The Acidic Moieties.—The phenylnaphthylglycollic acids were prepared from the corresponding naphthyl benzyl ketones; the α-naphthyl ketone was prepared by the method of Cook and Hewitt (*J.*, 1934, 376) and the β-naphthyl ketone by a similar reaction in nitrobenzene solution. The ketones were converted into *iso*nitrosoketones and the diketophenylnaphthylethanes converted into the glycollic acids by keeping them in ether solution with methyl-alcoholic potash.

α-Naphthyl* isonitrosobenzyl *ketone, yellow needles from benzene, m. p. 130—131° (Found: N, 4·9. $C_{18}H_{13}O_2N$ requires N, 5·1%). ***Diketophenyl-α-napthylethane***, m. p. 102—103°, from ethanol (Found: C, 82·8; H, 4·6. $C_{18}H_{12}O_2$ requires C, 83·1; H, 4·6%). ***Phenyl-α-naphthylglycollic acid*** crystallised from 50% (v/v) acetic acid in a hydrated form which began to lose water at 109° and melted with effervescence at 117°; on cooling the melt solidified and then melted at 146—147° (Found: C, 68·7; H, 6·0. $C_{18}H_{14}O_3,2H_2O$ requires C, 68·8; H, 5·7%). The anhydrous acid, m. p. 147—148°, was obtained by evaporating a benzene solution of the hydrated acid. With concentrated sulphuric acid the acid gave a greenish-yellow colour turning green.

β-Naphthyl* isonitrosobenzyl *ketone formed hexagonal plates from methanol, m. p. 159—160° (Found: N, 4·8. $C_{18}H_{13}O_2N$ requires N, 5·1%). ***Diketophenyl-β-naphthylethane*** formed needles from light petroleum, m. p. 88—89° (Found: C, 82·9; H, 4·7. $C_{18}H_{12}O_2$ requires C, 83·1; H, 4·6%). ***Phenyl-β-naphthylglycollic acid*** crystallised from benzene, m. p. 145—146°, and gave a greenish-blue colour turning mauve with concentrated sulphuric acid (Found: C, 77·6; H, 5·1. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·0%).

Esters.—The following basic esters are new. ***Dimethylaminoethyl benzilate***, prisms from light petroleum, m. p. 91—92° (Found: C, 72·2; H, 7·1. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·1%). Its ***hydrogen benzilate*** is formed (50% yield) by heating potassium benzilate and dimethylchloroethylamine hydrochloride in aqueous or alcoholic solution for 1 hour; prisms, sparingly soluble in alcohol, m. p. 159—160° (Found: C, 72·5; H, 6·3. $C_{32}H_{39}O_6N$ requires C, 72·8; H, 6·3%). ***Diethylaminoethyl benzilate***, prisms from light petroleum, m. p. 54° (Found: C, 73·5; H, 7·7. $C_{20}H_{25}O_3N$ requires C, 73·4; H, 7·7%). ***Methyl*-n-*propylaminoethyl benzilate hydrochloride***, m. p. 154°, from ethanol (Found: C, 66·3; H, 7·5. $C_{20}H_{26}O_3NCl$ requires C, 66·0; H, 7·2%). ***γ-Dimethylamino-ββ-dimethylpropyl benzilate***, long prisms from light petroleum, m. p. 66—67° (Found: C, 73·6; H, 7·9. $C_{21}H_{27}O_3N$ requires C, 73·9; H, 7·9%). ***Piperidinoethyl benzilate***, prisms from light petroleum, m. p. 71—72° (Found: C, 74·1; H, 7·4. $C_{21}H_{25}O_3N$ requires C, 74·3; H, 7·4%).

β-4-Benzilyloxy-1 : 2 : 2 : 6-tetramethylpiperidine, crystallized first from methanol and finally from acetone, formed needles, m. p. 155—156° (Found: C, 75·2; H, 8·0. $C_{32}H_{39}O_3N$ requires C, 75·2; H, 7·9%). The corresponding ***α-form*** of this ester crystallised from acetone in prisms, m. p. 137—138° (Found: C, 75·0; H, 8·0. $C_{32}H_{39}O_3N$ requires C, 75·2; H, 7·9%). ***4-Benzilyloxy-1 : 2 : 2 : 6 : 6-pentamethylpiperidine*** crystallised from light petroleum, m. p. 94° (Found: C, 75·4; H, 8·5. $C_{24}H_{31}O_3N$ requires C, 75·6; H, 8·2%).

The work, which is published by permission of the Director-General of Scientific Research (Defence), Ministry of Supply, was carried out while the authors were members of Sir Robert Robinson's team in the Dyson Perrins Laboratory, Oxford.

(A.H.F.-M.) Ministry of Supply C.D.R. Experimental Station, Porton, Wilts.
(H.R.I.) Department of Pharmacology, Oxford. [*Received, May 1st*, 1946.]

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12. *Some Products formed in the Reaction of* p-*Acetamidobenzenesulphonyl Azide with Pyridine.*

By J. N. Ashley, Geo. L. Buchanan, and (in part) A. P. T. Easson.

The reaction of *p*-acetamidobenzenesulphonyl azide with pyridine has been investigated, and four reaction products isolated. Three of these have been identified as N-(p-*acetamidobenzenesulphonimido*)*pyridine* (I; R = Ac), 4 : 4′-diacetamidobenzenesulphonanilide (II; R = Ac), and N^4-acetylsulphanilamide.

Curtius and Rissom (*Z. angew. Chem.*, 1913, **26**, 134) investigated the reaction of aromatic sulphonyl azides with aromatic hydrocarbons, and showed that sulphonamides were produced

according to the equation (1). Curtius and his co-workers continued their researches on the scope of the reaction where R = phenyl, substituted phenyl, and naphthyl, and R′ = phenyl,

$$R{\cdot}SO_2{\cdot}N_3 + R'H \longrightarrow R{\cdot}SO_2{\cdot}NHR' + N_2 \quad . \; . \; . \; . \; . \; . \; . \; (1)$$

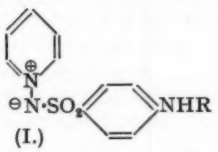
substituted phenyl, pyridyl, and quinolyl. Their results (*J. pr. Chem.*, 1921, **102**, 85; 1922, **106**, 66; 1925, **112**, 65, 88, 117; 1928, **120**, 89; 1930, **125**, 303) showed that the reaction was not always as simple as suggested in equation (1), but in most of the cases the reaction products were identified. In the case where R′ = pyridyl, compounds were isolated which were claimed to be substituted sulphonamidopyridines. Hydrolysis of these with hydrochloric acid yielded basic products which had the composition of aminopyridines but these were not identified; they were, however, characterised as mercuric chloride complexes or picrates. In one case only, where R = β-naphthyl, the evidence indicated, but not conclusively, formation of a substituted α-sulphonamidopyridine (*ibid.*, 1930, **125**, 303).

Curtius did not investigate the reaction between *p*-acetamidobenzenesulphonyl azide and pyridine, so it was decided to investigate this, as it appeared probable that it might afford an alternative method of preparation of 2-*p*-acetamidobenzenesulphonamidopyridine (*N*⁴-acetylsulphapyridine). While the work now described was in progress, Alamela and Ganapathi (*Current Sci.*, 1943, **12**, 119) reported that they had studied this reaction and obtained a product, m. p. 280°. They concluded that this was 3-*p*-acetamidobenzenesulphonamidopyridine since this m. p. was closer to that of the 3-isomeride (272—275°) than to those of the 2- and the 4-isomeride, m. p. 224—227° and 252°, respectively. No analytical or other data were given in support of this conclusion.

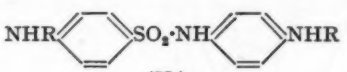
We found that when a solution of *p*-acetamidobenzenesulphonyl azide in a large excess of pyridine was boiled for 50—70 hours (in some cases Curtius employed several days; in others, 35 or 36 hours) a complex mixture of products was formed. Four products were readily isolated; the first (A) separated during the course of the reaction or on removal of some of the pyridine, the second (B) was obtained by addition of water to the concentrated pyridine solution, while the third (C) and fourth (D) crystallised out when the aqueous pyridine liquors were concentrated to a syrup. Although these four products account for only *ca.* 50% of the *p*-acetamidobenzenesulphonyl azide employed, the fate of the remainder has not yet been ascertained. It is hoped to report later on the examination of the dark red syrupy residue.

(A) is a colourless crystalline solid, m. p. 300°, insoluble in alkali but soluble in boiling water and in dilute mineral acids. The analytical data indicated the composition $C_{13}H_{13}O_3N_3S$, but the above properties eliminated the possibility that it was 2-, 3-, or 4-*p*-acetamidobenzenesulphonamidopyridine. Hydrolysis with boiling dilute alkali removed an acetyl group with formation of another crystalline compound, $C_{11}H_{11}O_2N_3S$, which was also insoluble in alkali, but very soluble in dilute acid. It contained a diazotisable amino-group, and was reconverted into (A) by acetylation.

Hydrolysis of (A), with dilute hydrochloric acid yielded sulphanilic acid and the hydrochloride of a base, $C_5H_6N_2$,HCl, m. p. 160°, not identical with any of the three known aminopyridine hydrochlorides, and which could be reconverted into (A) by treatment with *p*-acetamidobenzenesulphonyl chloride. Attempts to liberate the free base with sodium hydroxide, bicarbonate, or acetate resulted in formation of very dark resinous products with a distinct odour of pyridine.



(I.)



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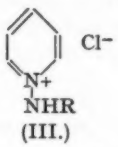

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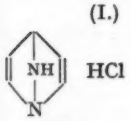
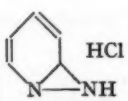
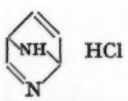


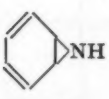
(IV.)



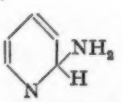
(V.)



(VI.)



(VII.)

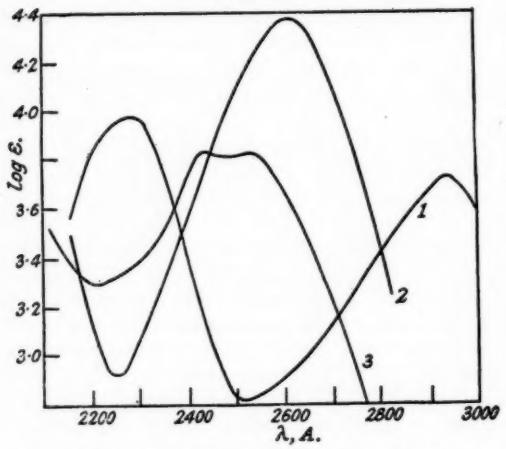


(VIII.)

When treated with nitrous acid the hydrochloride gave no diazo-reaction, but pyridine (identified as picrate) was liberated. Distillation with zinc dust and soda-lime gave ammonia and pyridine, and acetylation yielded a product which analysed for the hydrochloride of the monoacetylated base. A *picrate* was also obtained, and although all these compounds gave analytical data in agreement with derivatives of an aminopyridine they were not identical with the corresponding

derivatives of the three known aminopyridines. As the base hydrochloride apparently contained a pyridine or closely related ring, and an amino- or imino-group, two possibilities remained: (*a*) linkage through the pyridine nitrogen atom (III, R = H) and (*b*) bicyclic structures of the types (IV), (V), (VI). Although structure (V) is somewhat strained, it merits consideration, since it was shown by Curtius and Schmidt (*Ber.*, 1922, **55**, 1571, 1581) that sulphuryl azide $N_3 \cdot SO_2 \cdot N_3$ reacted with benzene and *p*-xylene to form bicyclic structures such as (VII).

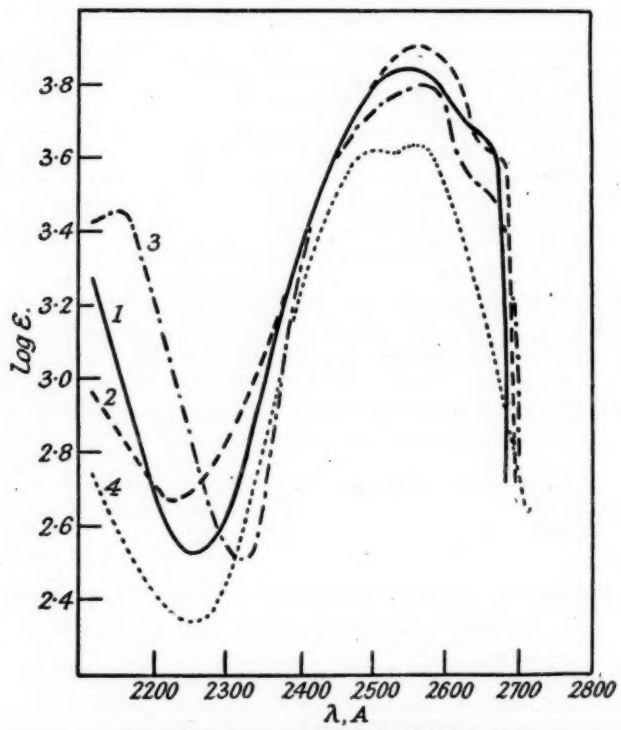
FIG. 1.



1. 2-*Aminopyridine hydrochloride in water* (0·04% *w./v.*).
2. 4- ,, ,, ,, ,, ,,
3. N- ,, ,, ,, ,, ,,

In an attempt to establish the type of linkage, the base hydrochloride was hydrogenated in aqueous solution by using Adams's catalyst. The reaction was stopped after a slow uptake of 6 atoms of hydrogen although hydrogenation was still proceeding extremely slowly. The reaction mixture contained ammonium chloride, pyridine (identified as picrate), and piperidine (identified as hydrochloride and picrate). This result can only be interpreted on formulæ (IV) and (VI) if it is assumed that the mild conditions of the hydrogenation were sufficient to break the C–N linkages.

FIG. 2.



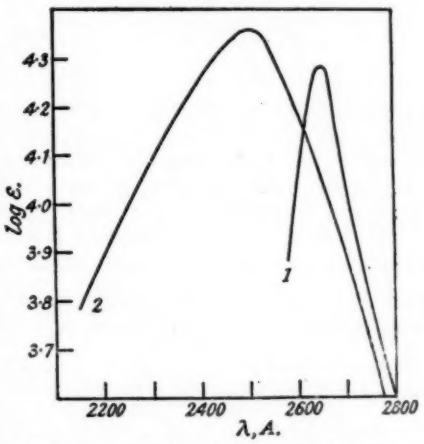
1—3. *As in Fig.* 1, *in* H_2SO_4 (0·02% *w./v.*).
4. *Pyridine in* H_2SO_4 (0·02% *w./v.*).

On the other hand, the result can readily be interpreted on formula (III) and even on (V). The latter might reasonably be expected to be reduced to 2-amino-1 : 2-dihydropyridine (VIII),

which could then either decompose into ammonia and pyridine or be hydrogenated to 2-aminopiperidine. The latter was shown by Kirsanov and Ivastchenko (*Bull. Soc. chim.*, **1936, 3,** 2279) to lose ammonia spontaneously with formation of Δ^2-tetrahydropyridine, which is then hydrogenated to piperidine.

By analogy with the work of Kirsanov and Ivastchenko (*loc. cit.*), who found that when the above hydrogenation was carried out in presence of excess of acetic anhydride the product was 2-acetamido-*N*-acetylpiperidine, an attempt was made to anchor the extra-nuclear nitrogen atom by carrying out the hydrogenation of the acetylated base hydrochloride (III; R = Ac) in acetic acid solution in presence of acetic anhydride. Hydrogenation ceased after rapid absorption of 6 atoms of hydrogen, and the product was proved by analysis to be a *monoacetamidopiperidine hydrochloride*. This fact that no new acetylatable group has been formed by hydrogenation is strongly in favour of structure (III) as against (V). Hydrolysis of this hydrogenation product with acid yielded the known *N*-aminopiperidine hydrochloride, and a direct comparison was made with an authentic sample, prepared as described by Knorr (*Annalen*, **1883, 221,** 299). Similarly, a synthetic sample of *N*-acetamidopiperidine hydrochloride was shown to be identical with the hydrogenation product. It therefore follows that the acetylated base hydrochloride which was hydrogenated should be N-*acetamidopyridinium chloride* (III; R = Ac), and the base hydrochloride is N-*aminopyridinium chloride* (III; R = H).

FIG. 3.

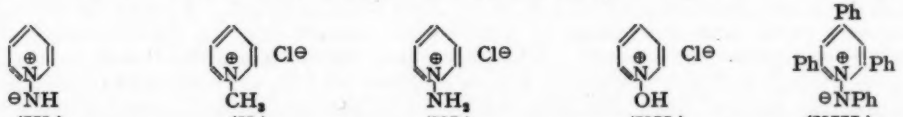


1. *In* n-*amyl alcohol.* 2. *In* H_2SO_4.

During the course of this work Dr. E. A. Braude, of the Imperial College of Science and Technology, kindly examined for us the ultra-violet light absorption of the base hydrochloride together with that of 2- and 4-aminopyridine for comparison, and independently suggested formula (III) from the results obtained in aqueous and concentrated sulphuric acid solutions. Dr. Braude reported: "In aqueous solution, the hydrochlorides are largely hydrolysed and the absorption is characteristic of the bases; it varies markedly with the position of the amino-substituent but the absorption of the isomeric base is similar to that of pyridine itself (Fig. 1). In concentrated sulphuric acid, the bases exist largely in the form of their salts and all exhibit light absorption closely resembling that of pyridine (Fig. 2), the auxochromic properties of the amino-group being almost completely lost by fixation of the free electron pair. The persistence of a low wave-length absorption in the case of the isomeric base also indicates the presence of the $N{\cdot}NR_2$ grouping."

All the evidence so far obtained supports the view that the base hydrochloride is represented by (III; R = H), and hence the free base, which was never isolated, must be (IX), while compound (A), which separated from the original reaction mixture, must be N-(p-*acetamidobenzenesulphonimido*)*pyridine* (I; R = Ac). Support for this formula is provided by the fact that the compound is insoluble in alkali since it contains no replaceable hydrogen atom, and by the ultra-violet absorption, also determined by Dr. Braude, which still shows typical pyridine-like absorption (Fig. 3).

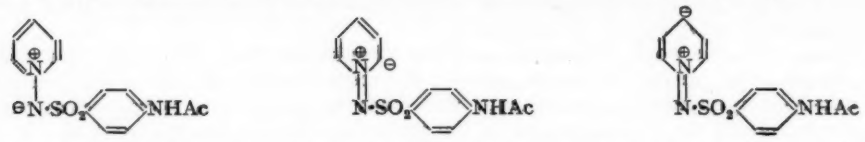
The formation of compounds of the type (III; R = H) and (I; R = Ac) is of theoretical interest since the former represents the hitherto undescribed member of the series (X, XI, and XII), while (I; R = Ac) is closely related to the type $R_3\overset{\oplus}{N}\text{–}\overset{\ominus}{N}{\cdot}SO_2R'$ which Mann and Pope (*J.*,



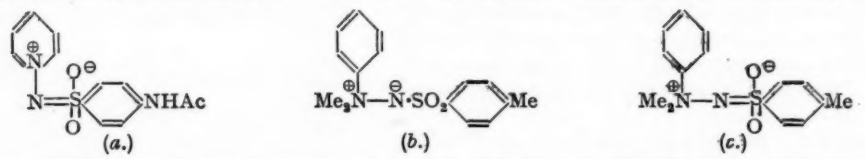
(IX.) (X.) (XI.) (XII.) (XIII.)

1922, **121,** 1052) attempted to prepare by the action of chloramine-T on dimethylaniline, and to the 2 : 4 : 6-triphenylpyridine-*N*-phenylimine (XIII) described by Schneider (*Annalen*, **1924, 438,** 115). Similarly to the related azoxysulphones described by Farrar and Gulland (*J.*, 1944, 368).

(I; R = Ac) conforms to the resonance requirements postulated by these authors. The resonance involving the N–N linkage is between structures such as the following:

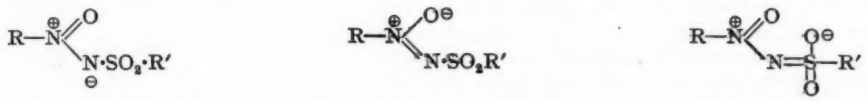


The stability of the compound can probably be attributed to this resonance. However, recent bond-length and dipole-moment determinations, *e.g.*, by Phillips, Hunter, and Sutton (*J.*, 1945, 146), show that the dative bond $\overset{+}{S}–\overset{-}{O}$ of sulphones, etc., should almost certainly be amended to S=O. Accordingly, it has been suggested by Mr. R. P. Bell, M.A., F.R.S. (private communication), that the main contributory resonance form of (I; R = Ac) should be represented by structure (*a*). This is a very attractive idea since it provides a much more



(*a*.) (*b*.) (*c*.)

plausible seat for the negative charge, but it should be pointed out that structure (*b*), which is incapable of ring resonance, is also capable of resonance of this type [*i.e.*, with structure (*c*)], though Mann and Pope (*loc. cit.*) failed to prepare this compound from the interaction of chloramine-T and dimethylaniline. This is, of course, negative evidence, but it suggests that resonance involving the N–S bond [*i.e.*, type (*a*)] is not *per se* responsible for the stability of (I; R = Ac). In this connection, it is noticeable that the pyridine-phenylimine (XIII) can only show ring resonance although, owing to the phenyl groups, a greater number of structures contribute, while the azoxysulphones, which are closely related to the general type $R_3\overset{+}{N}–\overset{-}{N}·SO_2R'$ show two types of resonance, *viz.*,



Compound (B), which was precipitated by water from the concentrated pyridine liquors, was readily soluble in alkali and insoluble in dilute acids. Hydrolysis with dilute alkali gave a product $C_{12}H_{13}O_2N_3S$ which was soluble in dilute acid and alkali, and contained one or more diazotisable amino-groups; on acetylation it yielded (B).

Hydrolysis of (B) with acid under pressure yielded sulphanilic acid and *p*-phenylenediamine. In accordance with this evidence, one would expect the product of alkaline hydrolysis to be (II, R = H) and compound (B) to be its diacetyl derivative, 4 : 4′-diacetamidobenzenesulphonanilide. The latter compound was synthesised by condensation of *p*-acetamidobenzenesulphonyl chloride with *p*-aminoacetanilide, and shown to be identical with (B). On hydrolysis with dilute mineral acid it yielded 4 : 4′-diaminobenzenesulphonanilide (II; R = H) identical with the product of alkaline hydrolysis of (B).

The formation of (II; R = Ac) in the reaction between pyridine and *p*-acetamidobenzenesulphonyl azide is of interest. It could readily arise from reaction of the azide with acetanilide, but the possibility of the latter's being present as an impurity in the crude sulphonyl chloride from which the azide was prepared was eliminated by the preparation and use of specially purified azide, the same yield of (II; R = Ac) then being obtained. It must therefore arise from 2 mols. of the azide. Although at present there is no evidence for the mechanism of this reaction, it is possible that the group $·SO_2N_3$ is replaced by the radical $R·SO_2·NH^-$ in the same way as the $·SO_3H$ group of sulphanilic acid is replaced by $·NO_2$ during nitration (Zincke and Kuchenbecker, *Annalen*, 1905, **339**, 226) and by Br during bromination (Schmitt, *ibid.*, 1861, **120**, 136). This suggestion does not account for the presence of the hydrogen atom in the $·SO_2·NH·$ grouping, but analogous reductions ($R·SO_2·N_3 \longrightarrow R·SO_2·NH_2$) are well known in this field [see compound (C), below]. It is noteworthy that the formation of compounds of type (II) was not recorded by Curtius and his co-workers.

Compound (C) was identified as N^4-acetylsulphanilamide. The formation of this product is not unexpected since Curtius (*J. pr. Chem.*, **1930**, **125**, 303) found that, besides the reaction represented by equation (1), an important side reaction was the conversion of the azide, $R{\cdot}SO_2{\cdot}N_3$, into the corresponding amide $R{\cdot}SO_2{\cdot}NH_2$. At present we are unable to state the source of this hydrogen; Curtius assumed that the azide first decomposed into the radical $R{\cdot}SO_2{\cdot}N<$ which then " abstracted " two atoms of hydrogen from the " solvent ". In some cases he was able to isolate the resulting oxidation product. Thus, after boiling benzenesulphonyl azide with aniline small amounts of benzidine in addition to the normal products were isolated from the reaction mixture (Bertho, *ibid.*, **1929**, **120**, 94).

Compound (D) was obtained in small amount only and has not yet been identified. Its empirical formula appears to be $C_{13}H_{15}O_3N_3S$.

N-(p-*Aminobenzenesulphonimido*)*pyridine* (I; R = H) exhibited no antibacterial activity when tested against *Staph. aureus* by the slide cell technique.

Further investigations of this reaction and in the sulphonyl azide field are in progress.

Experimental.

p-*Acetamidobenzenesulphonyl Azide.*—This was prepared from the corresponding sulphonyl chloride and sodium azide, as described by Curtius (*J. pr. Chem.*, **1926**, **112**, 117), *i.e.*, using aqueous alcohol as solvent, but although he claimed 93% yields, our yields varied between 62 and 79% of very crude product (m. p. *ca.* 100°). This could be recrystallised to give pure material agreeing with Curtius's m. p. of 107°, but as it was considered that the low yields were probably due to ester formation (and, indeed, in one instance we isolated ethyl *p*-acetamidobenzenesulphonate, m. p. 115°; no depression with a synthetic sample), the alcohol was replaced by acetone, giving consistent yields (77—81%) of the required product. *p*-Acetamidobenzenesulphonyl chloride (118 g.), dissolved in acetone (1500 c.c.), was treated with sodium azide (33 g.) in water (150 c.c.). The resulting mixture formed two layers and further amounts of water (350 c.c.) and acetone (150 c.c.) were required to give a homogeneous solution, which was kept for 3 hours at room temperature, and then poured into *ca.* 10 l. of water. The product had m. p. 109° (yield 95 g., 79%). Recrystallisation from benzene raised the m. p. to 113—114° (Found: N, 23·5. Calc. for $C_8H_8O_3N_4S$: N, 23·3%).

Condensation of p-*Acetamidobenzenesulphonyl Azide with Pyridine.*—The best results were obtained as follows: the azide (82 g.) was dissolved in pyridine (1·6 l.; dried over solid potassium hydroxide) and the solution refluxed gently for 65 hours. During this time the solution became dark brown and a solid (A) separated. The mixture was allowed to cool and this solid was filtered off. A little more was obtained by concentration. The total yield was 29 g. When the highly concentrated mother-liquor was poured into water a second product (B) (12·25 g.) separated. A mixed m. p. of purified samples of (A) and (B) (see later) gave a depression. Concentration of the aqueous pyridine liquor gave 8·85 g. of product (C), and further concentration to a thick syrup yielded 3·3 g. of crude product (D).

N-(p-*Acetamidobenzenesulphonimido*)*pyridine*, Compound (A) (I; R = Ac).—The crude product had m. p. *ca.* 270°, but repeated recrystallisation (charcoal) from hot water or aqueous alcohol gave pure crystals, colourless plates, m. p. 295—300° (decomp.) depending on rate of heating (Found: C, 53·6; H, 4·4; N, 14·3; S, 11·1. $C_{13}H_{13}O_3N_3S$ requires C, 53·6; H, 4·5; N, 14·45; S, 11·0%).

Alkaline hydrolysis of compound (A). The product (2·6 g.) was refluxed for 3 hours with aqueous sodium hydroxide (50 c.c., 20%) and a few c.c. of alcohol. The resulting solution was cooled, and long needles (1·8 g.), m. p. 230°, separated. Repeated recrystallisation (charcoal) from hot water gave N-(p-*aminobenzenesulphonimido*)*pyridine* (I; R = H), pale yellow needles, m. p. 235—236° (Found: C, 53·45; H, 4·65; N, 16·9; S, 13·1; *M*, 235. $C_{11}H_{11}O_3N_3S$ requires C, 53·0; H, 4·4; N, 16·9; S, 12·85%; *M*, 249). A small amount when acetylated with acetic anhydride and a few drops of sulphuric acid (*d* 1·84) gave a product, which after recrystallisation from water formed colourless plates, m. p. 290°, not depressed on admixture with compound (A).

Acid hydrolysis of compound (A). The product (3 g.) was refluxed for 2 hours with hydrochloric acid (30 c.c.; 1 : 1). On cooling, needles (1·2 g.) separated. This substance did not melt below 300°; it contained S and N, was soluble in acids and alkali, was a primary amine, and was identified as sulphanilic acid by conversion into monoethyl-orange by the method of Bernthsen and Goske (*Ber.*, 1887, **20**, 924). The mother-liquors from which the sulphanilic acid had separated were made strongly alkaline with potassium hydroxide, and extracted with ether and chloroform. During this operation both layers became deep red, and concentration of the extracts gave a dark red intractable gum (and a distinct odour of pyridine). Accordingly, an attempt was made to isolate the hydrochloride of the basic component and compound (A) (20·6 g.) was refluxed for 3 hours with hydrochloric acid (206 c.c.; 1 : 1). After removal of sulphanilic acid the filtrate was repeatedly concentrated and each batch of crystals separated. In this way two products were obtained: (i) 11·4 g. of sulphanilic acid, and (ii) 8·1 g. of colourless N-*aminopyridinium chloride*, m. p. 156°, which recrystallised from alcohol in stout colourless needles, m. p. 160° (Found: C, 45·7; H, 5·3; N, 21·6; Cl, 27·3. $C_5H_6N_2$,HCl requires C, 46·0; H, 5·4; N, 21·4; Cl, 27·2%). The *picrate* recrystallised from aqueous alcohol in fine yellow needles, and from alcohol in rhombs, m. p. 154—155° (Found: C, 41·1; H, 2·9; N, 21·5. $C_5H_6N_2$,$C_6H_3O_7N_3$ requires C, 40·9; H, 2·8; N, 21·7%). The chloride was very soluble in water and gave no reaction for a primary amine. Attempts to liberate the free base from the chloride with potassium carbonate or potassium acetate gave the dark red gum and the odour of pyridine encountered before.

Treatment of the chloride with acetic anhydride, and warming until solution occurred gave, on cooling, crystals of the *monoacetyl* derivative, m. p. 216°. These recrystallised from alcohol in stout

colourless needles, m. p. 222° (Found : C, 48·5; H, 5·4; N, 16·1; Cl, 20·1. $C_7H_8ON_2$,HCl requires C, 48·75; H, 5·2; N, 16·25; Cl, 20·6%).

A small amount of the chloride was intimately mixed with zinc dust and gently distilled. Ammonia was identified by smell, and a colourless liquid distilled over. This gave a picrate, m. p. 165°, undepressed on admixture with authentic pyridine picrate (m. p. 165—166°). Distillation with soda-lime gave an identical result.

The chloride (0·28 g.), dissolved in a small amount of water, was treated with 3 drops of hydrochloric acid (*d* 1·16) and sodium nitrite (0·15 g.). The solution was gently refluxed for a few minutes, diluted with water, and aqueous picric acid added. The resulting picrate, m. p. 166°, gave no depression with pyridine picrate.

Catalytic reductions. (*a*) *N*-Aminopyridinium chloride (2 g.), dissolved in distilled water (30 c.c.), was hydrogenated in presence of Adams's (PtO_2) catalyst (0·1 g.). After 8½ hours, almost 1100 c.c. of hydrogen (at 22°; 756 mm.) had been absorbed, and the reaction was stopped. The catalyst was filtered off, and a small sample of the clear, colourless filtrate treated with aqueous picric acid. The resulting picrate recrystallised from water in yellow needles, m. p. 149°, undepressed when mixed with authentic piperidine picrate, m. p. 149—150°.

The rest of the filtrate was made acid to litmus with hydrochloric acid and concentrated. Crystals appeared which were identified as ammonium chloride.

The mother-liquors, on further concentration, gave an oily solid, which was separated by treatment with alcohol into a very soluble portion and a less soluble solid. The soluble portion gave a picrate, m. p. 166°, which gave no depression in mixed m. p. with pyridine picrate. The less soluble solid had m. p. 222° and was probably piperidine hydrochloride (m. p. 232°), since it gave a picrate m. p. 149—150° which showed no depression in mixed m. p. with an authentic sample of piperidine picrate.

(*b*) *N*-Acetamidopyridinium chloride (1·5 g.), dissolved in acetic anhydride (10 c.c.) and glacial acetic acid (20 c.c.), was hydrogenated in presence of Adams's catalyst (0·2 g.). After 25 minutes, 680 c.c. of hydrogen had been absorbed at 22° and 765 mm., and uptake then ceased (Calc. for 6H : 670 c.c.). The solution was filtered from catalyst, and the solvent removed under reduced pressure. The residual pale green oil solidified when kept for 24 hours over potassium hydroxide in a vacuum. The pasty solid recrystallised from dioxan and gave yellow-green needles of *N-acetamidopiperidine hydrochloride*, m. p. 172—173° (0·9 g.; 58%) (Found : C, 47·1; H, 8·7; N, 15·2; Cl, 19·7. $C_7H_{14}ON_2$,HCl requires C, 47·1; H, 8·4; N, 15·7; Cl, 19·9%). This product (110 mg.) in hydrochloric acid (*d* 1·16; 3 c.c.) was heated on the steam-bath for 1 hour, concentrated, and the solid product recrystallised from alcohol, forming stout needles of *N*-aminopiperidine hydrochloride, m. p. and mixed m. p. 162—163°. The authentic sample was prepared by Knorr's method (*Annalen*, 1883, **221**, 299) and characterised as its benzoyl derivative (m. p. 198° from alcohol) and acetyl derivative (m. p., and mixed m. p. with hydrogenation product, 172—173°).

Re-synthesis of *N*-(*p*-acetamidobenzenesulphonimido)pyridine was effected as follows : *N*-Aminopyridinium chloride (1·35 g.) in water (2·5 c.c.) was treated with solid potassium carbonate until the solution was strongly alkaline, and some was left undissolved. This solution was then added to *p*-acetamidobenzenesulphonyl chloride (2·4 g.) in acetone (15 c.c.). Two layers were formed, and small amounts of water and acetone were added till a homogeneous solution was obtained. The solution was shaken for some time, and after standing overnight, the insoluble product was filtered off; 1·40 g., m. p. 270° (decomp.). Repeated recrystallisation from dilute ethanol gave colourless plates, m. p. 292—298° (depending on rate of heating) which gave no depression in mixed m. p. with authentic *N*-(*p*-acetamidobenzenesulphonimido)pyridine.

4 : 4′-*Diacetamidobenzenesulphonanilide* (Compound B), (II; R = Ac).—The crude compound had m. p. *ca.* 300°, and repeated recrystallisation from glacial acetic acid (charcoal) gave irregular buff-coloured micro-prisms, m. p. 308°. It was not analysed as it was difficult to purify completely. A mixed m. p. with compound (A) was markedly depressed.

The anilide (3 g.) was refluxed for 2 hours with aqueous sodium hydroxide (50 c.c.; 20%). This yielded the diamine (II; R = H), which crystallised from aqueous alcohol (charcoal) in colourless, light-sensitive needles, m. p. 138° (Found : C, 53·0, 53·1; H, 4·9, 5·0; N, 15·2; S, 12·4. Calc. for $C_{12}H_{13}O_2N_3S,\frac{1}{2}H_2O$: C, 53·0; H, 5·1; N, 15·45; S, 11·8%).

Hydrolysis of compound (B) with aqueous hydrochloric acid (1 : 1) gave sulphanilic acid and the diamine, m. p. 138°, and *p*-phenylenediamine was isolated after hydrolysis with hydrochloric acid (*d* 1·16) in a sealed tube at 120° for 6 hours.

There was no depression in mixed m. p. of compound (B) with authentic 4 : 4′-diacetamidobenzenesulphonanilide, m. p. 310° (micro-prisms from glacial acetic acid), prepared by condensation of 4-acetamidobenzenesulphonyl chloride with 4-aminoacetanilide (cf. E.P. 486,449; Webster and Powers, *J. Amer. Chem. Soc.*, 1939, **60**, 1553; Rubzow, *J. Gen. Chem. Russ.*, 1940, **10**, 831). The first two references give no m. p. for this compound, but Rubzow quotes m. p. 245—246°. Hydrolysis of this compound with dilute alkali gave 4 : 4′-diaminobenzenesulphonanilide (colourless needles, m. p. 138° from dilute alcohol), which was shown by mixed m. p. to be identical with the product of alkaline hydrolysis of compound (B). Webster and Powers (*loc. cit.*), Kolloff and Hunter (*J. Amer. Chem. Soc.*, 1940, **62**, 3355), and Ganapathi (*J. Indian Chem. Soc.*, 1938, **15**, 525) give 155—156° as the m. p. of 4 : 4′-diaminobenzenesulphonanilide, but Rubzow (*loc. cit.*), a number of patents (Swiss, 191,673; 199,682—4; Swedish, 90,259), and unpublished work from these laboratories give 136—138°. Recrystallisation of the product, m. p. 138°, from absolute alcohol gave the anhydrous compound, colourless plates, m. p. 155° (Found : C, 54·8; H, 5·1; N, 15·8; S, 12·3. Calc. for $C_{12}H_{13}O_2N_3S$: C, 54·75; H, 4·95; N, 16·0; S, 12·15%).

N^4-*Acetylsulphanilamide* (Compound C).—The crude material had m. p. *ca.* 200°. Recrystallisation from glacial acetic acid (charcoal) gave colourless needles, m. p. 219—220° (undepressed after admixture with N^4-acetylsulphanilamide), soluble in 2N-sodium hydroxide, and insoluble in 2N-hydrochloric acid and in aqueous sodium bicarbonate.

Compound (D).—The crude *compound* had m. p. 265—268°, and was insoluble in 2N-sodium hydroxide, but soluble in hydrochloric acid (*d* 1·16); it appeared to be partly soluble in 2N-hydrochloric acid. It was practically insoluble in boiling water, pyridine, glacial acetic acid, and the usual organic solvents but crystallised from aqueous pyridine or aqueous acetic acid in colourless prisms, m. p. 269° (decomp.) (Found: C, 53·15; H, 4·95; N, 14·45; S, 10·6, 11·3. $C_{13}H_{15}O_3N_3S$ requires C, 53·25; H, 5·1; N, 14·35; S, 10·95%).

The authors acknowledge their indebtedness to Dr. E. A. Braude for the ultra-violet absorption spectra determinations, to Mr. R. P. Bell, M.A., F.R.S., and Mr. G. Newbery, B.Sc., F.R.I.C., for much valuable discussion and criticism, to Mr. S. Bance, B.Sc., A.R.I.C., for the semimicro-analyses, and to the Directors of Messrs. May and Baker Ltd. for permission to publish these results.

THE RESEARCH LABORATORIES,
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13. *Researches in the Phenanthridine Series. Part VIII. Further Investigation of Trypanocidal Types.**

By LESLIE P. WALLS.

(With a Note by C. H. BROWNING, K. M. CALVER, and M. W. LECKIE.)

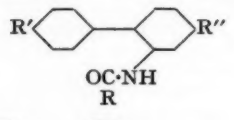
In Part VI (*J.*, 1945, 294) it has been shown that 9-phenylphenanthridinium salts with two amino-groups (cf. V; R = R′ = NH_2) exert a powerful chemotherapeutic action against *T. congolense*, whilst recently it has been further demonstrated (*Nature*, 1946, **157**, 263) that similar salts with carbethoxyamino- in place of amino-groups have some activity in *T. cruzi* infections. In this paper the effect has been studied of replacing the 9-phenyl by a 9-methyl group, and of substitution of (V) with other than amino-groups; thus in different compounds R = NH_2, NH·COMe, NH·CO_2Et, and R′ or R″ = NO_2, NH_2, NH·COMe, or NH·CO_2Et. The preparation of these types was achieved by ring-closure of the corresponding *o*-acylamido 4′-carbethoxyaminodiphenyls (I; R′ = NH·CO_2Et). This useful result is attributed to the electromeric character of the urethane group, and leads to the synthesis of (II; R = Me, R′ = NH_2, R″ = H), (II; R = Me, R′ = R″ = NH_2), and (X; R = NH_2, R′ = NO_2). The corresponding quaternary salts were readily prepared. The use of this method for the preparation of compounds with nitro- and carbethoxyamino-groups in the same molecule (cf. X; R = NH·CO_2Et, R′ = NO_2) provided a route to the quaternary salts with two different substituents referred to above. In salts with a 9-*o*-aminophenyl substituent it was not possible to convert the amino- into a carbethoxyamino-group, this failure being attributed to steric hindrance, for the 9-*p*-aminophenyl compounds readily reacted with ethyl chloroformate.

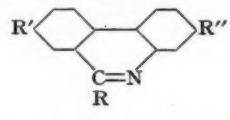
The effect of replacement of 9-phenyl by 9-methyl (cf. III; R′ = R″ = NH_2, R = Me or Ph) is to reduce the action on *T. congolense*. In the salts with mixed substituents it is found that the presence of an amino-group in the phenanthridine nucleus is essential to trypanocidal activity, which is enhanced when the 9-phenyl is substituted by *o*-, *m*-, or *p*-amino-, or by *o*- or *p*-nitro-groups.

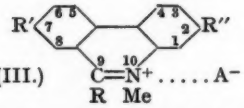
PREVIOUS work on this series has shown that in the synthesis of phenanthridines (cf. II) from acyl-*o*-xenylamines (cf. I) ring-closure is inhibited when R′ = NO_2 (Morgan and Walls, *J.*, 1932, 2225). This result was not unexpected in view of the well-known effect of a nitro-group in reducing the affinity of the positions in its ring for a kationic reagent, which the acylamido-group may be assumed to become in the presence of the normal condensing agent, phosphorus oxychloride. Indeed in (I; R = Me, R′ = NO_2, R″ = H) hydrolysis of the acetyl group proceeds much more rapidly under the reaction conditions than does ring-closure, and the yield of (II; R = Me, R′ = NO_2, R″ = H) is extremely small (*loc. cit.*). If derivatives of type (II; R = Me) are to become readily available it is clear that R′ must be a group possessing an opposite effect on substitution to the nitro-group; moreover it must be stable under the exacting reaction conditions, and in order to lead to substances likely to possess trypanocidal properties it must readily furnish an amino-group. While this work was in progress Petrow (*J.*, 1945, 19) showed how these desiderata could be satisfied by ring-closure of (I; R = Me, R′ = NH·COPh, R″ = H). The method recommended here is the location in the appropriate ring of a carbethoxyamino-group, which has a powerful electromeric effect in the opposite sense to that of the nitro-group, is very stable, and yet under appropriate conditions is readily derived from and converted into an amino-group. A further advantage with the more complex derivatives is that the melting points of carbethoxyamino-compounds are conveniently low and the solubility in organic solvents correspondingly high. That the proposed method is

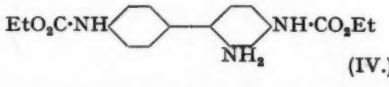
* The experimental work described in this paper formed the subject of British provisional patent applications Nos. 52/44 and 53/44.

strikingly successful may be exemplified by (I; R = Ph, R′ = R″ = NH·CO_2Et) which can be converted into the corresponding phenanthridine in over 50% yield by 15 minutes' heating with phosphorus oxychloride alone; by contrast the corresponding nitro-compound (I; R = Ph, R′ = R″ = NO_2) requires over 12 hours' heating with phosphorus oxychloride–nitrobenzene at 180° for the same degree of ring-closure. As shown in Part VII, the carbethoxyaminophenanthridine compounds thus produced can be converted into quaternary salts (cf. III; R = Ph, R′ = R″ = NH·CO_2Et) which can be hydrolysed quantitatively to the important diamino-quaternary salts. Certain of the carbethoxyl derivatives are also interesting therapeutically. This gives an alternative route to the preparation of " phenanthridinium

(I.) 

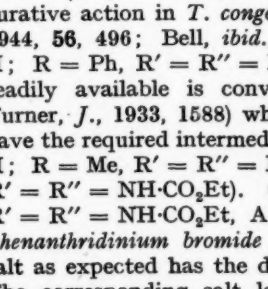
 (II.)





(IV.)

1553 " (III; R = Ph, R′ = R″ = NH_2, A = Br; *J.*, 1945, 294) which has shown marked curative action in *T. congolense* infection of cattle in Africa (Carmichael and Bell, *Vet. Rec.*, 1944, **56**, 496; Bell, *ibid.*, 1945, **57**, 449). The intermediate required for its synthesis is (I; R = Ph, R′ = R″ = NH·CO_2Et) and is prepared as follows: 2-nitrobenzidine which is readily available is converted into 2-nitro-4 : 4′-dicarbethoxyaminodiphenyl (Lesslie and Turner, *J.*, 1933, 1588) which is reduced to the non-basic amine (IV). Benzoylation of (IV) gave the required intermediate. The amine (IV) is likewise readily acetylated and the product (I; R = Me, R′ = R″ = NH·CO_2Et) is cyclised by phosphorus oxychloride to (II; R = Me, R′ = R″ = NH·CO_2Et). Conversion of this product into a quaternary salt (III; R = Me, R′ = R″ = NH·CO_2Et, A = $MeSO_4$) and finally hydrolysis to 2 : 7-*diamino*-9 : 10-*dimethylphenanthridinium bromide* (III; R = Me, R′ = R″ = NH_2, A = Br) readily follow. This salt as expected has the deep purple colour associated also with " phenanthridinium 1553 ". The corresponding salt lacking the 2-amino-group, 7-*amino*-9 : 10-*dimethylphenanthridinium bromide* (III; R = Me, R′ = NH_2, R″ = H, A = Br) has only a light red colour. For its preparation 2-acetamido-4′-carbethoxyaminodiphenyl (I; R = Me, R′ = NH·CO_2Et, R″ = H) is condensed in high yield to 7-*carbethoxyamino*-9-*methylphenanthridine*, which is hydrolysed to the amine identical with that described by Petrow (*loc. cit.*). Successive methylation and hydrolysis give the amino-quaternary salt (III; R = Me, R′ = NH_2, R″ = H, A = Br). The facile synthesis of carbethoxyamino-compounds of this series provides an opportunity of studying the chemotherapy of phenanthridinium salts with mixed substituents. There is described here a comprehensive series of such derivatives related to " phenanthridinium 897 " (V; R = R′ = NH_2, R″ = H) a substance which possesses a powerful remedial action in *T. congolense* infections, and to a new type (1588) 7-*amino*-9-*o*-*aminophenyl*-10-*methylphenanthridinium chloride* (V; R = R″ = NH_2, R′ = H).



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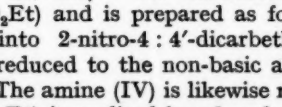

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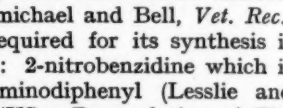

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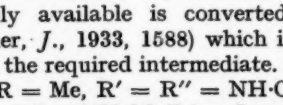
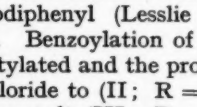


(VIII.)

(IX.)



(X.)

4-Nitro-2′-aminodiphenyl was prepared by an improved method which renders it readily accessible. The amino-group was smoothly carbethoxylated by the method of Lesslie and

Turner (*loc. cit.*) and then the nitro-group was reduced to give **2-*amino*-4'-*carbethoxyamino*-*diphenyl*** (VI). Condensation of this amine with *p*-nitrobenzoyl chloride yielded the acyl derivative (VII) which was smoothly and rapidly converted into **7-*carbethoxyamino*-9-*p*-*nitrophenylphenanthridine*** (VIII). The latter and the corresponding acetamido-compound were converted quantitatively into quaternary salts, from which was prepared a series of stable crystalline salts (V; R″ = H) in which R and R′ may be variously NH_2, NH·COMe, and $NH{\cdot}CO_2Et$.

The series related to the corresponding *o*-substituted derivatives was of particular interest, for both the corresponding *m*- and *p*- series had yielded quaternary salts with trypanocidal properties (*J.*, 1945, 294). **4-*Nitro*-2'-o-*nitrobenzamidodiphenyl*** could not be converted into the phenanthridine, but condensation of **2-o-*nitrobenzamido*-4'-*carbethoxyaminodiphenyl*** (IX; R = $NH{\cdot}CO_2Et$) to the corresponding phenanthridine (X; R = $NH{\cdot}CO_2Et$, R′ = NO_2) went smoothly, and conversion of the product into the quaternary salt provided a route to a similar series of salts (V; R′ = H).

In both these series the salts in which R = NH_2 were deep red; revealing the characteristic chromophoric effect of an amino-group in the 7-position.

Attempts to prepare the salts (V; R = R″ = $NH{\cdot}CO_2Et$, R′ = H) and (V; R = NH·COMe, R″ = $NH{\cdot}CO_2Et$, R′ = H) in which the carbethoxyamino-group occupies an *o*-position in the 9-phenyl ring from the corresponding salts in which R″ = NH_2 or R = R″ = NH_2 proved unsuccessful, although, as has been shown in Part VII, carbethoxylation of the amino-groups of quaternary salts of this series normally proceeds smoothly under very mild conditions. The chief contributory cause of this failure is probably steric hindrance, juxtaposition of the *o*-amino-group and the quaternary nitrogen group hindering access of the large chloroformate molecule. Acetylation of this *o*-amino-group was also inhibited; thus according to the experimental conditions **7-*amino*-9-o-*aminophenyl*-10-*methylphenanthridinium chloride*** (V; R = R″ = NH_2, R′ = H) could be mono-acetylated (on the 7-amino-group) or diacetylated, a particularisation that is not afforded by any of the other diamino-quaternary salt of this series yet investigated. It may also be due to steric causes that the nitro-group in quaternary salts with a 9-*o*-nitrophenyl substituent are not smoothly reduced in aqueous solution by iron powder, a method usually most efficaceous for nitro-quaternary salts.

*Note on Chemotherapeutic Trypanocidal Action.**—The present compounds (see Table) are complementary to those previously investigated (Walls, *J.*, 1945, 294; 1946, 1031) and comparisons are made here with the action of some of the latter. The same strains of *T. congolense* and *T. brucei* were employed.

(1) *T. brucei* is less susceptible than *T. congolense* to phenanthridine compounds; and a compound exhibiting a very high curative action against infections with *T. congolense* may show little or no effect on *T. brucei* in a dose 200 times as great (No. 1588). On the other hand, slight action on *T. brucei* may be associated with relatively weak action on *T. congolense* (No. 1600).

(2) While a phenyl group in the 9-position is not essential for trypanocidal action, analogues with a methyl group in that position are less active (cf. Nos. 1596—also the corresponding bromide and iodide—and 1505; 1605—also the corresponding bromide and iodide—and 1565, *J.*, 1945, 297).

(3) When one primary amino-group is present in the 7-position and another in the 9-phenyl ring, it is practically immaterial whether the latter amino-group occupies the *o*-, *m*-, or *p*-position, so far as concerns toxicity and action on *T. congolense* (Nos. 897, 1508, 1588, *loc. cit.*).

(4) The corresponding diacetamido-derivatives (Nos. 896, 1507, and 1589) are all of low trypanocidal power.

(5) The presence of a nitro- instead of amino-group in the phenyl ring causes only slight reduction in chemotherapeutic action (cf. Nos. 1586 and 897; 1587 and 1588).

(6) Carbethoxyamino- and, still more markedly, acetamido- replacing the primary amino-group in the phenanthridine ring reduces the therapeutic action, while as a rule slightly decreasing toxicity (cf. Nos. 1600 with 1596 and the corresponding bromide and iodide; 1598 and 1581 with 1605; 1592 and 1593 with 897; 1579 and 1590 with 1588; and in previous results 1566 with 1565).

(7) When one amino-group of Nos. 897 and 1588 is replaced by carbethoxyamino- and the other by acetamido- the chemotherapeutic action is very weak (Nos. 1594, 1595, 1591).

* Work done with the support of the Medical Research Council in the Department of Bacteriology, The University and Western Infirmary, Glasgow.

Compound.	Formula (III). Substituents.	Acid radical.	Therapeutic effect in mice infected with *T. congolense* (Strain 1).* Dose in mg.‡	Result.§	*T. brucei*.† Dose in mg.‡	Result.§
1600	7-NH·CO_2Et-9-Me	Br	3·3—2	Cure	3·3	Slight
			1	Slight		
1596	7-NH_2-9-Me	Cl	1—0·5	Cure	1	0
			0·2	(Cure)		
			0·066	Slight		
1605	2 : 7-NH_2-9-Me	Cl	2—0·2	Cure	1	Slight
			0·1	(Cure)	0·2	0
			0·05	Marked—Slight		
1598	2 : 7-NH·CO_2Et-9-Me	Cl	1·66	Cure	1·66	Slight
			0·83—0·55	(Cure)		
1581	2 : 7-NH·COMe-9-Me	Cl	4	0	4	0
1593	7-NH·COMe-9-*p*-C_6H_4·NH_2	$MeSO_4$	4	Cure	4	0
			2	Slight		
1595	7-NH·COMe-9-*p*-C_6H_4·NH·CO_2Et	Cl	4	Cure	4	0
			2	Slight		
1592	7-NH·CO_2Et-9-*p*-C_6H_4·NH_2	Cl	2—0·2	(Cure)	2	0
			0·1	Slight		
1594	7-NH·CO_2Et-9-*p*-C_6H_4·NH·COMe	Cl	4	Marked	4	0
1586	7-NH_2-9-*p*-C_6H_4·NO_2	Cl	2—0·033	Cure	2	Slight
			0·017	Marked		
1590	7-NH·COMe-9-*o*-C_6H_4·NH_2	Cl	0·5	0	0·5	0
1579	7-NH·CO_2Et-9-*o*-C_6H_4·NH_2	Cl	2—0·1	Cure	2	0
			0·066	(Cure)		
			0·033	0		
1591	7-NH·CO_2Et-9-*o*-C_6H_4·NH·COMe	Cl	5	Cure	5	0
			1·66	0		
1587	7-NH_2-9-*o*-C_6H_4·NO_2	Cl	1·43—0·066	Cure	1·43	0
			0·033	Marked		
			0·017	Slight		
1588	7-NH_2-9-*o*-C_6H_4·NH_2	Cl	0·2—0·02	Cure	2	0
			0·01	(Cure)		
			0·007	Slight		
1589	7-NH·COMe-9-*o*-C_6H_4·NH·COMe	Cl	3·3	0	3·3	0

* See Browning and Calver, *J. Path. Bact.*, 1943, **55**, 393; Calver, *Trop. Dis. Bull.*, 1945, **42**, 704; treatment was given at the acme stage.

† See Browning *et al.*, *J. Path. Bact.*, 1934, **39**, 75; 1938, **46**, 203; the strain of trypanosome used was "Paris III" and treatment was given 24 hours after inoculation.

‡ Dosage is reckoned per 20 g. of body weight, 1 c.c. of solution being injected subcutaneously: the highest dose shown is not less than half the average maximum tolerated.

§ The terms used to designate degrees of trypanocidal action are as follows:

Cure = Complete sterilisation of infection.
(Cure) = Cure effected only in a proportion of the animals treated.
Marked = Absence of parasites from blood for 10 days or longer.
Slight = Disappearance of parasites from blood for several days.
0 = No effect.

Summary. (a) Quaternary phenanthridine compounds containing two primary amino-groups, one at least of which is situated in the phenanthridine nucleus, constitute the most powerful chemotherapeutic agents known against *T. congolense*.

(b) Reduction of trypanocidal action is produced by substitution in the amino-group or groups of the phenanthridine part of the molecule.

(c) It has been observed previously that where amino-groups are restricted to the 9-phenyl ring trypanocidal action is weak (Nos. 206, 207, III; R′ = R″ = H, R = C_6H_4·NH_2; 1052, III; R′ = R″ = H, R = $C_6H_3(NH_2)_2$, Morgan and Walls, *J.*, 1931, 2445). Accordingly it would appear that the presence of at least one amino-group in the phenanthridine part is the most important factor for trypanocidal activity: however, no compound containing such a group along with a substituted amino-group in the 9-phenyl ring has yet been examined.

Experimental.

2-Acetamido-4′-carbethoxyaminodiphenyl.—To a solution of 4-amino-2′-acetamidodiphenyl (10 g., 1 mole; Petrow, *loc. cit.*) and diethylaniline (7·1 ml., 1·01 mole) in boiling alcohol (50 ml.) ethyl chloroformate (3·5 ml., 1·01 mole) was slowly added. After the vigorous reaction had subsided the solution was refluxed for 30 minutes and then poured into 200 ml. of N-hydrochloric acid. The crystalline *product*, obtained thus in high yield, was washed with dilute hydrochloric acid and then with water. It recrystallised from spirit in white leaves, m. p. 161° (Found: N, 9·45. $C_{17}H_{18}O_3N_2$ requires N, 9·4%).

7-Amino-9-methylphenanthridine.—The foregoing compound (6·5 g.) and phosphorus oxychloride (13 ml.) were gently refluxed for 1 hour, there being vigorous evolution of hydrogen chloride during the first 15 minutes. The solution was carefully stirred into ice-water to decompose excess of phosphorus oxychloride and ammonia was added to neutrality. The solid product was purified by dissolving it in cold N-sulphuric acid, separating a small amount of insoluble amorphous matter, and adding alkali to precipitate *7-carbethoxyamino-9-methylphenanthridine* as a gum which slowly set to a white solid (5·2 g.); crystallisation from spirit yielded colourless leaves, m. p. 210·5° (Found: C, 73·0; H, 5·85; N, 10·35. $C_{17}H_{16}O_2N_2$ requires C, 72·85; H, 5·7; N, 10·0%). Hydrolysis was effected by the method of Lesslie and Turner (*loc. cit.*); water (5 ml.) was added to a solution of the carbethoxyamino-compound (2 g.) in concentrated sulphuric acid (10 ml.). The temperature was raised to 150° and kept there for 15 minutes, vigorous effervescence ensuing.

After being cooled the solution was poured into water and neutralised by ammonia to liberate 7-amino-9-methylphenanthridine which crystallised from a large volume of spirit in almost white needles, m. p. 232° (Found: N, 13·25. Calc. for $C_{14}H_{12}N_2$: N, 13·45%). On being heated with acetic anhydride followed by dilution with water and neutralisation by ammonia, it was converted into the acetyl derivative, m. p. 247·5° (Found: N, 11·3. Calc. for $C_{16}H_{14}ON_2$: N, 11·2%).

7-Carbethoxyamino-9 : 10-dimethylphenanthridinium Bromide (1600).—7-Carbethoxyamino-9-methylphenanthridine (11 g.) in nitrobenzene (80 ml.) at 150° was converted by methyl sulphate (7 ml.) into the orange methosulphate. The product was characterised as the *bromide*, which crystallised from water in deep yellow plates, m. p. 230° (decomp.) (Found: N, 7·05; Br, 19·5; loss at 100°, 8·85. $C_{18}H_{19}O_2N_2Br,2H_2O$ requires N, 6·8; Br, 19·45; H_2O, 8·75%).

7-Amino-9 : 10-dimethylphenanthridinium Chloride (1596).—7-Acetamido-9-methylphenanthridine was similarly converted into the *methosulphate* which crystallised from water in clumps of yellow needles, m. p. 270—272° (decomp.) (Found: C, 57·15; H, 5·35; S, 8·7. $C_{18}H_{20}O_5N_2S$ requires C, 57·45; H, 5·3; S, 8·5%). Hydrolysis with hot 5N-hydrochloric acid followed by neutralisation and addition of potassium iodide gave brownish-red crystals of *7-amino-9 : 10-dimethylphenanthridinium iodide* (1571), m. p. 261° (decomp.) (Found: N, 8·0; I, 35·85. $C_{15}H_{15}N_2I$ requires N, 8·0; I, 36·25%). The *chloride*, which is extremely soluble in water, is formed by double decomposition of the iodide with a boiling aqueous suspension of silver chloride. Evaporation of the filtrate to dryness left a gum which was converted by hot alcohol into a mass of brown prisms, m. p. 260° (decomp.) (Found: Cl, 13·3. $C_{15}H_{15}N_2Cl$ requires Cl, 13·7%). The *bromide* (1597) crystallised from water in orange-red needles, m. p. 269° (decomp.) (Found: Br, 26·35. $C_{15}H_{15}N_2Br$ requires Br, 26·4%).

2-Amino-4 : 4′-dicarbethoxyaminodiphenyl (IV).—Well-powdered 2-nitro-4 : 4′-dicarbethoxyaminodiphenyl (5·5 g.) was heated with water (20 ml.), hydrochloric acid (1 drop), and reduced iron (5·5 g.). After 1 hour the mixture was extracted with boiling spirit. The filtrate was distilled to small bulk, the non-basic *amino*-compound crystallising out in white acicular prisms, m. p. 186° (Found: C, 62·9; H, 6·15: N, 12·4. $C_{18}H_{21}O_4N_3$ requires C, 63·0; H, 6·1; N, 12·25%). When the amine was dissolved in acetic anhydride the *acetyl* compound crystallised in small white needles, m. p. 199° (Found: N, 10·95. $C_{20}H_{23}O_5N_3$ requires N, 10·9%).

2 : 7-Dicarbethoxyamino-9-phenylphenanthridine.—A solution of the foregoing amino-compound (36 g.) in nitrobenzene (100 ml.) at 150° was treated with benzoyl chloride (10·5 ml.), hydrogen chloride being evolved. After 30 minutes at this temperature, the solution was cooled and then diluted with 2 volumes of spirit. The *benzoyl* compound which separated (35 g.) recrystallised from spirit in colourless prisms, m. p. 147° (Found: C, 66·85; H, 5·6; N, 9·45. $C_{25}H_{25}O_5N_3$ requires C, 67·1; H, 5·6; N, 9·4%). This product (20 g.) was refluxed gently for 1 hour with phosphorus oxychloride (40 ml.) by which time evolution of hydrogen chloride had ceased and the solution had become yellow. On being stirred into dilute aqueous ammonia the reaction mixture was converted into a granular yellow solid, which was dissolved in 150 ml. of spirit, treated with a few drops of ammonia to discharge the orange colour, and finally with 40 ml. of water. Flocculent yellowish needles of *2 : 7-dicarbethoxyamino-9-phenylphenanthridine* (13·2 g.) separated, a product surprisingly readily soluble in alcohol, but sparingly soluble in benzene. For purification advantage was taken of its slightly basic character. It was dissolved in nitrobenzene (90 ml.) and a stream of dry hydrogen chloride led into the solution, a complex with the latter being precipitated in minute yellow crystals. When a solution of this complex in alcohol was treated with dilute ammonia the base crystallised, sometimes in prisms. Recrystallisation from toluene gave prisms, and from aqueous methyl alcohol, needles, m. p. 222° (efferv.) (Found for solvent-free compound: C, 69·8; H, 5·3; N, 9·9. $C_{25}H_{23}O_4N_3$ requires C, 70·0; H, 5·25; N, 9·8%).

2 : 7-Dicarbethoxyamino-9-phenyl-10-methylphenanthridinium methosulphate crystallised in high yield when the foregoing substance, dissolved in nitrobenzene at 160°, was treated with a small excess of methyl sulphate, orange plates being formed, m. p. 278° (decomp.) (Found: N, 7·35; S, 5·8. $C_{27}H_{29}O_8N_3S$ requires N, 7·55; S, 5·75%). The corresponding chloride was identical with that described in the previous paper.

The methosulphate (1 g.) was dissolved in sulphuric acid (2 ml. of concentrated acid, 1 ml. of water) and heated at 135° for 20 minutes. On dilution with water and partial neutralisation a red *acid sulphate* crystallised (Found for dried salt: S, 11·85. $(C_{20}H_{18}N_3)_2SO_4.2{\cdot}5H_2SO_4$ requires S, 11·9%). It was dissolved in water, potassium bromide added, and the solution neutralised with ammonia; characteristic purple prisms of 2 : 7-diamino-9-phenyl-10-methylphenanthridinium bromide crystallised (*J.*, 1945, 294).

2 : 7-Diamino-9-methylphenanthridine.—2-Acetamido-4 : 4′-dicarbethoxyaminodiphenyl (5 g.) and phosphorus oxychloride (10 ml.) reacted vigorously with separation of a yellow crystalline precipitate. After decomposition of excess of acid chloride with water and neutralisation a pale yellow solid was obtained which was dissolved in 50 ml. of pyridine. An equal volume of hot water was added, and with cooling an almost white micro-crystalline precipitate formed (3·7 g.). Recrystallisation from nitrobenzene gave almost colourless needles of *2 : 7-dicarbethoxyamino-9-methylphenanthridine*, m. p. 253° (efferv.) (Found: C, 65·7; H, 5·85; N, 11·6. $C_{20}H_{21}O_4N_3$ requires C, 65·4; H, 5·7; N, 11·45%). Hydrolysis with sulphuric acid followed by neutralisation yielded the *diamino*-compound which crystallised from

a large volume of alcohol in yellow plates, m. p. 265·5° (Found: C, 75·2; H, 6·05; N, 18·6. $C_{14}H_{12}N_2$ requires C, 75·35; H, 5·9; N, 18·85%). The *acetyl* compound formed white needles, m. p. 323—326° (decomp.) (Found: N, 13·3. $C_{15}H_{17}O_2N_3$ requires N, 13·7%).

2 : 7-*Diamino*-9 : 10-*dimethylphenanthridinium Bromide* (1580).—Reaction in nitrobenzene at 160° of 2 : 7-dicarbethoxyamino-9-methylphenanthridine with methyl sulphate gave 2 : 7-*dicarbethoxyamino*-9 : 10-*dimethylphenanthridinium methosulphate* (1582) in yellow prisms, unmolten at 320°, soluble in water but best recrystallised from alcohol (Found for dried salt: N, 8·85; S, 6·65. $C_{22}H_{27}O_8N_3S$ requires N, 8·5; S, 6·5%). The *chloride* (1598) crystallised from aqueous alcohol in microscopic yellow prisms unmolten at 320° (Found: Cl, 8·5. $C_{21}H_{24}O_4N_3Cl$ requires Cl, 8·5%). Aqueous solutions of these salts are liable to supersaturation and to setting as gels. 2 : 7-*Diacetamido*-9 : 10-*dimethylphenanthridinium chloride* (1581) was similarly prepared; orange needles, unmolten at 320° (Found: N, 12·0; Cl, 9·75. $C_{19}H_{20}O_2N_3Cl$ requires N, 11·75; Cl, 9·9%). Hydrolysis of either of these salts gave acid solutions from which on addition of potassium bromide and neutralisation 2 : 7-*diamino*-9 : 10-*dimethylphenanthridinium bromide* crystallised, m. p. 283° (Found for dried salt: N, 13·45; Br, 24·6. $C_{15}H_{16}N_3Br$ requires N, 13·2; Br, 25·15%). The *chloride* (1605) formed purple plates, m. p. 278°, extremely soluble in water (Found: Cl, 12·95. $C_{15}H_{16}N_3Cl$ requires Cl, 12·95%). The *iodide* (1606) formed sparingly soluble dark purple felted needles, m. p. 293° (Found: I, 34·95. $C_{15}H_{16}N_3I$ requires I, 34·8%).

2-*Nitro*-4′-*aminodiphenyl*.—*p*-Nitrodiphenyl (20 g.) was nitrated according to Bell and Kenyon (*J.*, 1926, 2707) and the crude mixture of dinitro-compounds (26 g.) was extracted thrice with 100 ml. of boiling spirit. The undissolved residue (12 g.) was practically pure 4 : 4′-dinitrodiphenyl, and from the extract a mixture (*ca.* 12 g.) of this substance and 2 : 4′-dinitrodiphenyl was obtained. Separation of the latter was not attempted, the mixture being employed in the next stage of partial reduction. The methods described in the literature (cf. Finzi and Bellavita, *Gazzetta*, 1934, **64**, 335) are unsuitable except for the preparation of small quantities of nitro-amine, but that used by Purdie (*J. Amer. Chem. Soc.*, 1941, **43**, 2276) for the partial reduction of 2 : 2′-dinitrodiphenyl was profitably adapted. The mixture of nitro-compounds was dissolved in boiling alcohol (180 ml.), and the solution was treated with sodium polysulphide prepared from flowers of sulphur (3·6 g.), crystalline sodium sulphide (14 g.), and water (45 ml.). After 3 hours' refluxing the solution was left overnight and then poured into water. The rather sticky red precipitate was dissolved in hot N-hydrochloric acid (180 ml., charcoal); on being cooled the solution filled with white felted needles of the hydrochloride of 2-nitro-4′-aminodiphenyl, by-products remaining in solution. The salt was washed with cold dilute hydrochloric acid, dissolved in hot water, and the solution basified to liberate the amine as a red oil which soon crystallised (7 g.). This product was pure enough for the purpose, but could be recrystallised from spirit in red prisms, m. p. 100° (Found: N, 13·25. Calc. for $C_{12}H_{10}O_2N_2$: N, 13·1%).

2-*Amino*-4′-*carbethoxyaminodiphenyl* (VI).—The foregoing nitroamine (7 g.) was converted into 2-*nitro*-4′-*carbethoxyaminodiphenyl* by the method described for the preparation of 2-acetamido-4′-carbethoxyaminodiphenyl. The product (7 g.) crystallised from spirit in transparent yellow plates, m. p. 105·5° (Found: C, 62·85; H, 4·8; N, 10·0. $C_{15}H_{14}O_4N_2$ requires C, 62·9; H, 4·9; N, 9·8%). It was reduced by an equal weight of reduced iron in acidified aqueous suspension. Extraction of the reaction mixture with hot spirit followed by removal of the solvent gave the *amine*, which was extremely soluble in alcohol, benzene, and dilute mineral acid. It recrystallised from petrol–benzene in transparent buff plates, m. p. 98° (Found: C, 70·5; H, 6·25; N, 11·05. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·25; N, 10·95%).

7-*Carbethoxyamino*-9-p-*nitrophenylphenanthridine* (VIII).—2-Amino-4′-carbethoxyaminodiphenyl (27 g.) was condensed in hot pyridine solution (88 ml.) with *p*-nitrobenzoyl chloride (23 g.). The product (44·5 g.) liberated by dilution of the reaction mixture with N-sulphuric acid was extracted with dilute sodium carbonate solution, and the residue was dissolved in boiling spirit. After separation of a small amount of insoluble material and cooling, 2-p-*nitrobenzamido*-4′-*carbethoxyaminodiphenyl* (36 g.) crystallised in transparent yellow prisms, sometimes accompanied by needles, m. p. 184° (Found: C, 65·45; H, 4·75; N, 10·65. $C_{22}H_{19}O_5N_3$ requires C, 65·3; H, 4·7; N, 10·35%). The following method of ring-closure gave the best result. The acyl compound (21·5 g.), nitrobenzene (72 ml.), and phosphorus oxychloride (43 ml.) were heated in a bath at 150—160° for 1 hour and then stirred into ice-cold dilute aqueous ammonia. The solid *product* (12·8 g.) was separated from the nitrobenzene and washed successively with water, a little nitrobenzene and spirit. Crystallisation from pyridine afforded clumps of feathery yellow needles, but transparent prisms were obtained from chlorobenzene, m. p. 254° (Found: C, 68·3; H, 4·4; N, 11·0. $C_{22}H_{17}O_4N_3$ requires C, 68·25; H, 4·4; N, 10·85%). Steam-distillation of the nitrobenzene mother-liquor furnished a further quantity of the product which was best purified at the next stage. Reaction of the product in nitrobenzene solution with methyl sulphate afforded 7-*carbethoxyamino*-9-p-*nitrophenyl*-10-*methylphenanthridinium methosulphate*, which crystallised from water in transparent orange prisms, m. p. 209° (decomp.) (Found: N, 8·05; S, 5·75; loss at 100°, 3·25. $C_{24}H_{23}O_8N_3S,H_2O$ requires N, 7·9; S, 6·0; H_2O, 3·4%). The *chloride* was readily obtained from this salt, or by the action of ethyl chloroformate on the aqueous solution of the nitroamino-quaternary salt (see below). It crystallised from the reaction mixture in transparent yellow prisms, m. p. 243° (decomp.) (Found: N, 9·5; Cl, 8·0. $C_{22}H_{20}O_4N_3Cl$ requires N, 9·6; Cl, 8·1%).

7-*Amino*-9-p-*nitrophenylphenanthridine* was obtained by sulphuric acid hydrolysis of the urethane. It crystallised from nitrobenzene in red plates, m. p. 279° (Found: C, 72·5; H, 4·25; N, 13·5. $C_{19}H_{13}O_2N_3$ requires C, 72·4; H, 4·15; N, 13·3%). When a solution of the amine in pyridine was treated with acetic anhydride the *acetyl* compound crystallised in lemon-yellow needles; recrystallised from alcohol, m. p. 282° (Found: C, 68·4; H, 4·9; N, 10·1. $C_{21}H_{15}O_3N_3,C_2H_6O$ requires C, 68·5; H, 5·15; N, 10·4%). This compound afforded an almost quantitative yield of 7-*acetamido*-9-p-*nitrophenyl*-10-*methylphenanthridinium methosulphate*, which crystallised from water in talc-like yellow crystals, m. p. 267·5° (decomp.) (Found for dried salt: N, 8·5; S, 6·45. $C_{23}H_{21}O_7N_3S$ requires N, 8·7; S, 6·6%).

7-*Acetamido*-9-p-*aminophenyl*-10-*methylphenanthridinium Methosulphate* (1593).—A hot aqueous solution of the foregoing salt was rapidly reduced by iron powder, the filtrate depositing orange-yellow prisms of the *amino*-salt, m. p. 258° (decomp.) (Found for dried salt: N, 9·4; S, 7·3. $C_{23}H_{23}O_5N_3S$ requires N, 9·25; S, 7·05%). Acetylation with hot acetic anhydride afforded the diacetamido-salt previously described (*J.*, 1938, 395), and reaction of its aqueous solution with ethyl chloroformate converted it quantitatively into 7-*acetamido*-9-p-*carbethoxyaminophenyl*-10-*methylphenanthridinium chloride* (1595) which crystallised from water in golden-yellow plates, m. p. 200—206° (decomp.) (Found: N, 8·0; Cl, 6·75; loss at 100°, 12·15. $C_{25}H_{24}O_3N_3Cl,3·5H_2O$ requires N, 8·2; Cl, 6·9; H_2O, 12·3%).

7-*Carbethoxyamino*-9-p-*aminophenyl*-10-*methylphenanthridinium chloride* (1592) was the product of reduction of the corresponding nitro-compound in aqueous solution with iron powder, transparent orange prisms being obtained from alcohol, m. p. 297—300° (decomp.) (Found: N, 10·45; Cl, 8·45. $C_{23}H_{22}ON_3Cl$ requires N, 10·3; Cl, 8·7%). Acetylation of this salt afforded 7-*carbethoxyamino*-9-p-*acetamidophenyl*-10-*methylphenanthridinium chloride* (1594), which resembled the corresponding diacetyl and dicarbethoxyl salts in crystallising from water in two forms, *viz.*, transparent yellow prisms and microscopic needles, m. p. 213° (decomp.) (Found for dried salt: N, 9·25; Cl, 7·85. $C_{25}H_{24}O_3N_3Cl$ requires N, 9·35; Cl, 7·9%).

7-*Amino*-9-p-*nitrophenyl*-10-*methylphenanthridinium Chloride* (1586).—The corresponding acetamido-salt (2·5 g.) was hydrolysed by heating its solution in sulphuric acid (5 ml. of concentrated acid, 2·5 ml. of water) at 125° for 15 minutes. On being diluted with water the solution deposited white crystals of an acid salt, but neutralisation by ammonia and addition of sodium chloride caused dark red transparent plates of the *nitroamino*-salt to crystallise; m. p. 242° (decomp.) (Found for dried salt: N, 12·0; Cl, 9·5. $C_{20}H_{16}O_2N_3Cl$ requires N, 11·5; Cl, 9·7%).

4-*Nitro*-2′-*o*-*nitrobenzamidodiphenyl* crystallised from glacial acetic acid in buff plates, m. p. 230—231° (Found: N, 11·4. $C_{19}H_{11}O_4N_3$ requires N, 11·6%). Heating with phosphorus oxychloride caused profound decomposition, and from the product no crystalline substance could be isolated.

7-*Carbethoxyamino*-9-*o*-*nitrophenylphenanthridine*.—2-Amino-4′-carbethoxyaminodiphenyl (10 g.) in boiling chlorobenzene solution (50 ml.) condensed with *o*-nitrobenzoyl chloride (7·8 g.) to yield 2-*o*-*nitrobenzamido*-4′-*carbethoxyaminodiphenyl*, which crystallised (13·5 g.) from the cold reaction mixture and gave on recrystallisation from spirit almost colourless acicular prisms (10 g.), m. p. 197° (Found: C, 65·1; H, 4·6; N, 10·4. $C_{22}H_{19}O_5N_3$ requires C, 65·3; H, 4·7; N, 10·4%). Although the crude product which crystallised from the chlorobenzene reaction mixture contained a little diacyl compound it could be used without recrystallisation for the next stage. The product of reaction of the acyl compound (10 g.) and phosphorus oxychloride (20 ml.) on the steam-bath for 1 hour was liberated by cold dilute aqueous ammonia. It was purified from tarry matter by filtration of its solution in benzene (250 ml.) through a column (11 cm. × 2·5 cm. diam.) of alumina (B.D.H., for chromatographic analysis), elution being completed with a further 150 ml. of benzene. Impurities were strongly adsorbed at the top of the column, and the golden-yellow filtrate after evaporation to 100 ml. yielded bright yellow needles of 7-*carbethoxyamino*-9-*o*-*nitrophenylphenanthridine* (6 g.), m. p. 199° (Found: C, 68·4; H, 4·25; N, 11·3. $C_{22}H_{17}O_4N_3$ requires C, 68·25; H, 4·4; N, 10·95%); on methylation in nitrobenzene it gave 7-*carbethoxyamino*-9-*o*-*nitrophenyl*-10-*methylphenanthridinium methosulphate*, which crystallised from water in transparent yellow plates, m. p. 226° (decomp.) (Found: N, 7·65; S, 5·55; loss at 100°, 6·75, 6·35. $C_{24}H_{23}O_8N_3S,2H_2O$ requires N, 7·65; S, 5·8; H_2O, 6·55%).

7-*Amino*-9-*o*-*nitrophenylphenanthridine* was obtained by hydrolysis of the carbethoxyamino-compound with sulphuric acid. Sparingly soluble in benzene or alcohol, it crystallised from chlorobenzene in brown transparent prisms, m. p. 230° (Found: C, 71·85; H, 4·1; N, 13·2. $C_{19}H_{13}O_2N_3$ requires C, 72·3; H, 4·1; N, 13·3%). A paste of the amine (5 g.) in hot glacial acetic acid (10 ml.) was treated with acetic anhydride(4 ml.) whereupon solution rapidly took place followed by separation of the *acetyl* compound in clumps of white prisms, m. p. 287·5° (Found: C, 70·3; H, 4·3; N, 11·9. $C_{21}H_{15}O_3N_3$ requires C, 70·6; H, 4·25; N, 11·75%).

7-*Acetamido*-9-*o*-*nitrophenyl*-10-*methylphenanthridinium methosulphate* gave deep yellow talc-like crystals from water, m. p. 283° (decomp.) (Found: N, 8·5; S, 6·3; loss at 100°, 3·6. $C_{25}H_{21}O_7N_3S,H_2O$ requires N, 8·4; S, 6·4; H_2O, 3·6%).

7-*Acetamido*-9-*o*-*aminophenyl*-10-*methylphenanthridinium Chloride* (1590).—Reduction of the foregoing nitro-salt with iron powder was not satisfactory, and the following method was used. A boiling suspension of the salt (2 g.) in alcohol (40 ml.) was treated with stannous chloride (3·2 g.) and concentrated hydrochloric acid (2·8 ml.). When a clear solution had been obtained dilute ammonia was added to neutralise it partially and then alcohol was evaporated. On being cooled the solution deposited crystals of the *amino*-salt, which on recrystallisation from water furnished deep yellow matted needles (1 g.), m. p. 271·5° (decomp.) (Found: N, 9·95; Cl, 8·4; loss at 100°, 7·7. $C_{23}H_{20}ON_3Cl,2H_2O$ requires N, 10·15; Cl, 8·6; H_2O, 8·7%).

7-*Carbethoxyamino*-9-*o*-*aminophenyl*-10-*methylphenanthridinium Chloride* (1579).—Again, reduction of the corresponding nitro-salt with iron powder was unsatisfactory, but readily took place in alcoholic solution with stannous chloride. Addition of water to the reaction mixture caused the *product* to crystallise in an almost quantitative yield of small brown prisms which were purified by recrystallisation from water; m. p. 272° (decomp.) (Found: N, 9·9; Cl, 8·25; loss at 100°, 4·2. $C_{23}H_{22}O_2N_3Cl,H_2O$ requires N, 9·85; Cl, 8·35; H_2O, 4·25%).

From the solution of this salt in acetic anhydride golden yellow needles of 7-*carbethoxyamino*-9-*o*-*acetamidophenyl*-10-*methylphenanthridinium chloride* (1591) crystallised. On recrystallisation from water this salt had m. p. 203—205° (decomp.) (Found: N, 8·75, Cl, 7·2; loss at 100°, 7·65. $C_{25}H_{24}O_3N_3Cl,2H_2O$ requires N, 8·65; Cl, 7·3; H_2O, 7·4%).

7-*Amino*-9-*o*-*nitrophenyl*-10-*methylphenanthridinium Chloride* (1587).—7-Carbethoxyamino-9-*o*-nitrophenyl-10-methylphenanthridinium methosulphate was hydrolysed by sulphuric acid, and the reaction mixture diluted with water and neutralised by ammonia to liberate a sulphate as a red oil which slowly

crystallised. The corresponding *chloride* crystallised from water in red prisms which had the surprisingly low m. p. 86° (Found for dried salt: N, 11·65; Cl, 9·5. $C_{20}H_{16}O_2N_2Cl$ requires N, 11·5; Cl, 9·7%).

7-Amino-9-o-aminophenyl-10-methylphenanthridinium Chloride (1588).—A solution of the foregoing nitro-amino-salt in water was heated for 30 minutes with an equal weight of iron powder. The red filtrate was made just alkaline with sodium carbonate, separated from an amorphous red precipitate, neutralised with hydrochloric acid, and distilled under reduced pressure to small bulk. On being cooled the solution deposited ruby-red prisms of the *diamino*-salt, m. p. *ca.* 158° (decomp.) (Found: N, 11·4; Cl, 9·65; loss at 100°, 7·8. $C_{20}H_{18}N_3Cl$, $1·5H_2O$ requires N, 11·6; Cl, 9·8; H_2O, 7·45%).

When an aqueous solution of this salt was stirred with ethyl chloroformate an orange precipitate formed, which on crystallisation from water gave 7-carbethoxyamino-9-*o*-aminophenyl-10-methylphenanthridinium chloride. Likewise when the salt was heated with acetic anhydride it was converted into 7-acetamido-9-*o*-aminophenyl-10-methylphenanthridinium chloride, which is almost insoluble in acetic anhydride. When either the latter compound or the diamino-salt was heated in glacial acetic acid solution with acetic anhydride no product crystallised, but, on addition of water and sodium chloride the diacetylated salt, *7-acetamido-9-o-acetamidophenyl-10-methylphenanthridinium chloride* (1589) crystallised in buff plates, m. p. 240·5° (decomp.) (Found: N, 8·8; Cl, 7·2; loss at 100°, 14·7. $C_{24}H_{22}O_2N_3Cl,3H_2O$ requires N, 8·55; Cl, 7·2; H_2O, 14·6%).

The work described above has been carried out as part of the Research programme of the Chemical Research Laboratory, and the paper is published by permission of the Director of the Laboratory.

CHEMICAL RESEARCH LABORATORY,
DEPT. OF SCIENTIFIC AND INDUSTRIAL RESEARCH,
TEDDINGTON, MIDDLESEX.

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14. *Viscosities of Aqueous Solutions of Amino-acids, with Some Conductivity Values.*

By A. E. BELL and W. M. MADGIN.

Jones and Talley (*J. Amer. Chem. Soc.*, 1933, **55**, 624) have concluded that viscosity–concentration considerations classify dissolved substances into non-electrolytes, showing a linear relationship and a continuous increase of viscosity with concentration, and electrolytes, which show deviation from linearity and ultimately lower the viscosity below that of pure water. Solutions of amino-acids have now been examined to see if such ampholytes exhibit the properties of either of these two classes or if they show distinctive class properties of their own.

Although viscometrically glycine and alanine appear to be non-electrolytes this is not considered to suggest the non-existence of dual ions.

Sulphanilic acid and betaine hydrochloride are included for comparison and seem to behave similarly to electrolytes. Certain conductivity values are included and appear to agree with the viscosity conclusions.

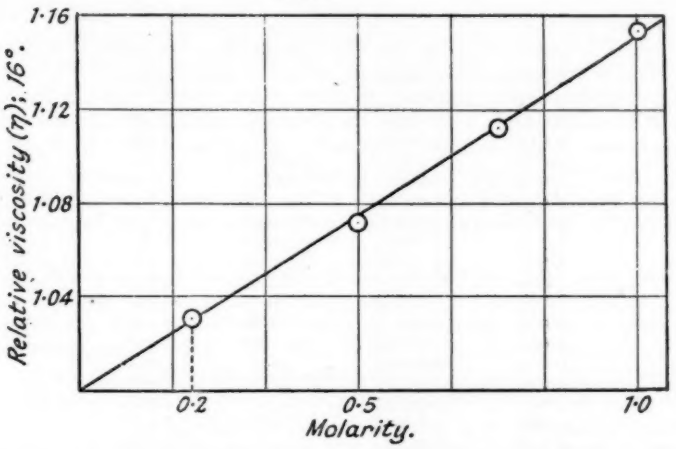
GLASSTONE ("Text Book of Physical Chemistry", Macmillan, London, 1940) states that simple aliphatic amino-acids are thought to exist in solutions mainly in the form of dual ions and he quotes $K_a = 5 \times 10^{-3}$ for the acidic dissociation constant of glycine, on the assumption that a considerable proportion of dual ions exist. On general grounds such dual ions might be expected to produce effects similar to strong electrolytes, the viscosity–concentration peculiarites of which are attributed by Jones and Talley (*loc. cit.*) to inter-ionic effects of the kind envisaged by the Debye–Hückel theory. The present investigations sought to show if dual ions did produce such effects. Glycine and alanine were selected as examples which would be expected to be similar, and sulphanilic acid and betaine hydrochloride were included as ampholytes of marked one-sided weakness which might allow of useful comparison. No previous data exist apart from a few isolated measurements of solutions of glycine and alanine by Hedestrand (*Z. anorg. Chem.*, 1922, **124**, 153) and we have substantially confirmed these.

The table gives our values for concentrations, densities, and relative viscosities of solutions. Fig. 1 shows a linear variation of relative viscosity with concentration of glycine up to 1·0 M at 16°. Similar linearity is shown by glycine solutions at 40° and by alanine solutions at 16°. Evidently, these solutions behave as the non-electrolytes of Jones and Talley (*loc. cit.*) but the non-existence of dual ions does not necessarily follow. It may be that the positive and negative charges on a dual ion are so close together that the distortion of the ionic atmosphere by a shearing force perpendicular to the direction of the velocity gradient (see Falkenhagen, "Electrolytes", Oxford Univ. Press, 1934) does not occur and may be nullified by the superimposition of atmospheres appropriate to a positive and a negative ion. Thus the usual unequal distribution of charge in the ionic atmosphere may not exist.

Viscosities of 2·0M-glycine at 16° and 40° are much greater than would be expected by

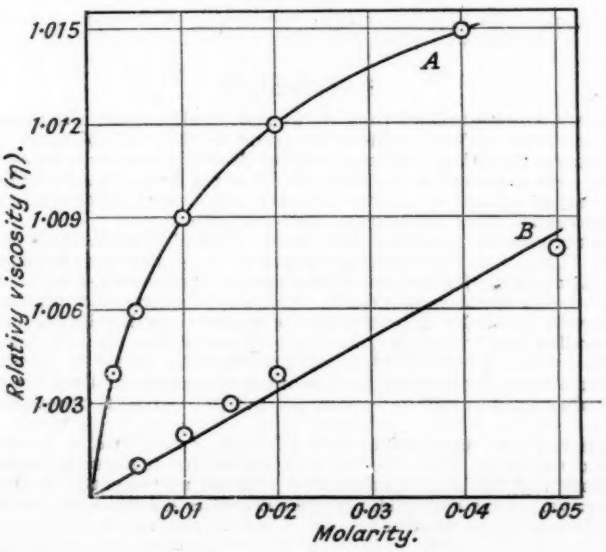
extrapolating curves as in Fig. 1. These greater values, whilst differing from the non-electrolytes of Jones and Talley (*loc. cit.*), certainly do not in any way resemble the electrolytes which these authors report as ultimately lowering viscosity at quite small concentrations. 2·0M-Glycine is a concentrated solution in which some new factors probably become operative. Fig. 2 shows sulphanilic acid (*A*) to differ from glycine (*B*) and non-electrolytes but to resemble the strong

FIG. 1.



electrolyte potassium bromate (Jones and Talley, *loc. cit.*) although neither with sulphanilic acid nor with potassium bromate is there an ultimate concentration at which the viscosity begins to decrease. The concentration ranges investigated may have been insufficient, but solubility limitations prevented further study of sulphanilic acid. Betaine hydrochloride gives viscosity variations similar to sulphanilic acid and both show some resemblance to strong electrolytes but

FIG. 2.



differ from non-electrolytes. Thus the four amino-acids under review appear to fall into two groups, with glycine and alanine in one group and sulphanilic acid and betaine hydrochloride in the other. It was thought that conductivity data might help to confirm this classification, but there do not seem to be any data except for some equivalent conductivity values for sulphanilic acid by Boyle (*J.*, 1919, **115**, 1505).

We have therefore made some measurements of equivalent conductivity and our results are given in the table. They appear to confirm the conclusions from the viscosity, *viz.*, that glycine and alanine are virtually non-conductors, but the other two acids, whilst less than strong electrolytes, are definite conductors of the same order as, *e.g.*, chloroacetic acid. Allowance being made for the difference in temperature of investigation, our results for sulphanilic acid are in fair agreement with those of Boyle (*loc. cit.*).

		Density.		Relative viscosity (η).*		Equiv. conductivity (ohm^{-1})
	M.	At 16°.	At 40°.	At 16°.	At 40°.	at 18°.
Glycine	0·0025	0·99893	—	1·0005	—	—
	0·005	0·99912	—	1·001	—	—
	0·010	0·99921	—	1·002	—	0·085
	0·015	0·99937	—	1·003	—	—
	0·020	0·99955	0·99275	1·004	1·003	0·043
	0·050	1·00050	0·99375	1·008	1·008	0·023
	0·080	1·00180	0·99450	1·013	1·012	—
	0·100	1·00220	0·99525	1·015	1·015	0·013
	0·150	1·00360	0·99660	1·022	1·023	—
	0·200	1·00550	0·99820	1·029	1·031	0·077
	0·500	1·01508	1·00755	1·071	1·076	—
	0·750	1·02309	—	1·112	—	—
	1·000	1·03110	1·02260	1·153	1·165	—
	2·000	1·06097	1·05204	1·359	1·713	—
Alanine	0·010	0·99920	—	1·003	—	0·071
	0·020	0·99950	—	1·005	—	0·050
	0·050	1·00017	—	1·016	—	0·037
	0·100	1·00082	—	1·030	—	0·032
	0·200	1·00326	—	1·056	—	0·027
Betaine hydrochloride	0·010	—	—	—	—	41·0
	0·020	0·99960	—	1·014	—	36·0
	0·050	1·00090	—	1·020	—	29·0
	0·100	1·00220	—	1·028	—	23·0
Sulphanilic acid †	0·0025	0·99841	—	1·004	—	88·64
	0·005	0·99863	—	1·006	—	64·10
	0·010	0·99911	—	1·009	—	48·70
	0·020	0·99983	—	1·012	—	36·70
	0·040	1·00166	—	1·015	—	27·10

* $\eta = \eta_s/\eta_0$, where η_s = viscosity of solution, η_0 = viscosity of water.
† Data for density and η relate to 20°.

Experimental.

" AnalaR " Glycine was recrystallised from water and dried in a vacuum desiccator. Pure alanine was twice dissolved in water and crystallised by addition of ½ vol. of ethyl alcohol. " AnalaR " Sulphanilic acid was recrystallised from boiling water and dried to constant weight in a vacuum desiccator. Betaine hydrochloride was dissolved in a minimum of warm concentrated hydrochloric acid, cooled under water, and an equal volume of acetone added slowly. Further cooling gave a deposit of fine crystals which were vacuum-filtered and dried at 100° for 2½ hours.

The determinations of relative viscosities and densities were by the methods described by Glass and Madgin (*J.*, 1934, 145, 1124), their No. 2 viscometer and silica pyknometers being used. Each viscosity value in the table is the average of three concordant results (agreeing to ± 0·001) and this has required many measurements because of the rapid growth of moulds in amino-acid solutions (especially at 40°). Even before these growths are visible they give rise to marked irregularities, and therefore freshly made samples of solutions are frequently necessary for repeat experiments. During actual use the viscometer was sealed (cf. Applebey, *J.*, 1910, **97**, 2000) to exclude dust and, as far as possible, to avoid infection by spores. Guard filters were placed on either side of the viscometer and a short circuit air tube joined them. The temperature variation was ± 0·05° at 16° and 20°, but, in the prevailing supply conditions, it was ± 0·20° at 40°.

Conductivity measurements were made with a simple metre bridge, a valve oscillator, and a non-inductively wound resistance box. No more is claimed for the results than that they are of the right order of magnitude; in the case of sulphanilic acid fair agreement with Boyle (*loc. cit.*) is noted above. Since no other values are available, the present results are of use to enable a comparison to be made among the four compounds concerned.

Clifton College, Bristol.
King's College (Durham University), Newcastle upon Tyne. [*Received, May 9th*, 1946.]

15. *The Reduction of* 1 : 1′-*Azonaphthalene and of Some* 4 : 4′-*Derivatives.*

By Herbert H. Hodgson and John Habeshaw.

A preparation of 1 : 1′-diamino-2 : 2′-dinaphthyl is described and the ease of ring closure to 1 : 2 : 7 : 8-dibenzocarbazole is further exemplified in the reduction of some 4 : 4′-disubstituted-1 : 1′-azonaphthalenes.

The work of Nietzki and Goll (*Ber.*, 1885, **18**, 3253) and of Cumming and Steele (*J.*, 1923, 2464) on the reduction of 1 : 1′-azonaphthalene has been confirmed. The very satisfactory method of Cohen and Oesper (*Ind. Eng. Chem. Anal.*, 1936, **8**, 306) for preparing naphthidine, has now been found by suitable modification to afford about 10% of 1 : 1′-diamino-2 : 2′-dinaphthyl and about 40% of 1 : 2 : 7 : 8-dibenzocarbazole. The high yield of the dibenzocarbazole indicates that the initial transformation of 1 : 1′-hydrazonaphthalene in the acid medium would appear to afford approximately equal amounts of 1 : 1′-diamino-2 : 2′-dinaphthyl and 4 : 4′-diamino-1 : 1′-dinaphthyl; ease of ring closure, however, converts about 80% of the former into the dibenzocarbazole.

The facile ring closure of 1 : 1′-diamino-2 : 2′-dinaphthyl has now been further exemplified by the reduction with acid stannous chloride in ethyl alcohol of 4 : 4′-dinitro-, 4 : 4′-dichloro-, and 4-*nitro*-4′-*methoxy*-1 : 1′-*azonaphthalene*, each of which affords a moderate yield of the corresponding *dibenzocarbazole* but no detectable 4 : 4′-disubstituted-1 : 1′-diamino-2 : 2′-dinaphthyl; the remainder of the reduction products are simple α-naphthylamine derivatives. When alcohol is absent from the reduction mixture, complete fission takes place at the azo-group with production of 4-substituted-α-naphthylamines. From 4 : 4′-nitro- and 4-nitro-4′-methoxy-1 : 1′-azonaphthalene the *hydrochlorides* of 3 : 6-diamino- and 3-amino-6-methoxy-1 : 2 : 7 : 8-dibenzocarbazole were obtained, but the free bases were too susceptible to oxidation for their preservation.

Experimental.

Reduction of 1 : 1′-*Azonaphthalene.*—The azo-compound (20 g.) was reduced by stannous chloride in ethyl alcohol and hydrochloric acid according to the directions of Cohen and Oesper (*loc. cit.*), and their process for separating the 4 : 4′-diamino-1 : 1′-dinaphthyl hydrochloride followed. After this had been filtered off, the filtrate was diluted with water (200 c.c.) and the white precipitate of crude 1 : 2 : 7 : 8-dibenzocarbazole (8 g.) removed and dried; it crystallised from benzene in colourless needles, m. p. 216° (Bucherer and Schmidt, *J. pr. Chem.*, 1909, **79**, 375, give m. p. 216°) (Found : N, 5·2. Calc. for $C_{20}H_{13}N$: N, 5·2%), which gave a reddish-brown solution with concentrated sulphuric acid. When solutions of the carbazole and picric acid in xylene were mixed together, 1 : 2 : 7 : 8-dibenzocarbazole picrate separated; this crystallised from benzene in red needles, m. p. 239° (Veselý, *Ber.*, 1905, **38**, 139, gives m. p. 238·5°) (Found : N, 11·5. Calc. for $C_{26}H_{16}O_7N_4$: N, 11·3%). The filtrate after removal of the carbazole was rendered alkaline by adding powdered sodium hydroxide until the precipitated tin salts were redissolved, after which the white insoluble residue of 1 : 1′-diamino-2 : 2′-dinaphthyl (2 g.) was removed and washed with water; it crystallised from benzene in colourless plates, m. p. 278—279° (Nietzki and Goll, *loc. cit.*, give m. p. 273°) (Found : N, 10·1. Calc. for $C_{20}H_{16}N_2$: N, 9·9%), which were readily soluble in dilute hydrochloric acid.

Reduction of 4 : 4′-*Dinitro*-1 : 1′-*Azonaphthalene.*—The azo-compound (5 g.) was dissolved in glacial acetic acid (250 c.c.) and reduced with stannous chloride and hydrochloric acid by the method of Nietzki and Goll (*loc. cit.*), and the mixture poured into water. The yellow precipitate (3·5 g.) was dried, dissolved in sufficient hot nitrobenzene to maintain dissolution at room temperature, and the solution saturated with hydrogen chloride and kept overnight. The yellow precipitate of 3 : 6-*dinitro*-1 : 2 : 7 : 8-*dibenzocarbazole* (1·2 g.) was insoluble in the usual solvents but separated from hot nitrobenzene in yellowish micro-crystals which sintered at *ca.* 385° (Found : N, 12·0. $C_{20}H_{11}O_4N_3$ requires N, 11·8%). Attempted reduction of 4 : 4′-dinitro-1 : 1′-azonaphthalene in alkaline or neutral media produced only insoluble tars. When, however, a suspension of the compound (5 g.) in gently boiling ethyl alcohol (75 c.c.) was treated gradually with a solution of stannous chloride (25 g.) in hydrochloric acid (25 c.c., *d* 1·16), dissolution occurred after about 75% of the reducing mixture had been added. The mixture was refluxed gently for 1 hour, then cooled and kept overnight; 3 : 6-*diamino*-1 : 2 : 7 : 8-*dibenzocarbazole dihydrochloride* separated as a white powder (1·6 g.) which was filtered off and washed with ether; it decomposed at *ca.* 360—370° (Found : Cl, 19·4. $C_{20}H_{18}N_3$,2HCl requires Cl, 19·2%). When to a boiling solution of 3 : 6-dinitro-1 : 2 : 7 : 8-dibenzocarbazole (1 g.) (see above) in glacial acetic acid solution was added a solution of stannous chloride (5 c.c.) in hydrochloric acid (5 c.c., *d* 1·16), a fairly vigorous reaction ensued and, on cooling, the above dihydrochloride (0·3 g.) separated (Found : Cl, 19·2%); a similar result was obtained when the 4 : 4′-dinitro-1 : 1′-azonaphthalene was reduced in glacial acetic acid solution with excess of stannous chloride and hydrochloric acid, but neither method is preferable to that described above. When a solution of the dihydrochloride (1 g.) in hydrochloric acid (5 c.c., *d* 1·16) and water (10 c.c.) was tetrazotised at 5° by addition of sodium nitrite (0·55 g.) dissolved in the minimum of water, and then boiled for 90 minutes on the water-bath with ethyl alcohol (150 c.c.), 1 : 2 : 7 : 8-dibenzocarbazole was obtained on removal of the alcohol, and, after two recrystallisations from benzene, was obtained in colourless needles, m. p. 216° (Found : N, 10·1%).

Reduction of 4 : 4′-dinitro-1 : 1′-azonaphthalene (2 g.) by crystallised stannous chloride (10 g.) dissolved in hydrochloric acid (20 c.c., *d* 1·16) gave 1 : 4-naphthylenediamine, which was isolated by dilution of the reaction mixture with water (25 c.c.) and addition of solid sodium hydroxide until the tin compounds had dissolved; the mixture was then filtered rapidly, and the solid residue boiled with a mixture of glacial acetic acid (20 c.c.) and acetic anhydride (5 c.c.) for a few minutes, filtered, and diluted with water. The precipitated diacet-1 : 4-dinaphthylenediamide crystallised from dilute acetic acid in white needles, m. p. 304—305° (Kleeman, *Ber.*, 1886, **19**, 334, gives m. p. 304°) (Found: N, 11·8. Calc. for $C_{14}H_{14}O_2N_2$: N, 11·6%).

Reduction of 4 : 4′-*Dichloro*-1 : 1′-*azonaphthalene*.—The azo-compound (1 g.) was reduced according to the directions of Nietzki and Goll (*loc. cit.*) in hot glacial acetic acid solution with stannous chloride and hydrochloric acid. No hydrochloride separated from the solution on cooling, but on pouring it into water a white precipitate of 3 : 6-*dichloro*-1 : 2 : 7 : 8-*dibenzocarbazole* formed. After several crystallisations from acetic acid it was obtained in colourless plates, m. p. 228—230° (Found: Cl, 20·8. $C_{20}H_{11}NCl_2$ requires Cl, 21·1%). When the dihydrochloride of 3 : 6-diamino-1 : 2 : 7 : 8-dibenzocarbazole (2 g.) was diazotised at 5° as above, and the filtered solution added to one of cuprous chloride (5 g.) in hydrochloric acid (50 c.c.), a vigorous reaction ensued which was completed by heating for 30 minutes on the water-bath. The precipitate was filtered off, washed with dilute ammonia to remove copper salts, and crystallised 4 times from acetic acid; 3 : 6-dichloro-1 : 2 : 7 : 8-dibenzocarbazole was thus obtained as slightly coloured plates, m. p. 226—228°, mixed m. p. with previous preparation, 227—229° (Found: Cl, 20·9%). When the azo-compound (2 g.) was reduced with stannous chloride and hydrochloric acid as above, and the reduction mixture made alkaline and steam distilled, 4-chloro-1-naphthylamine (0·5 g.) was obtained; this crystallised from light petroleum in colourless needles, m. p. 98° (Reverdin and Crépieux, *Ber.*, 1900, **33**, 682, give m. p. 98°) (Found: Cl, 19·8. Calc. for $C_{10}H_8NCl$: Cl, 20%); the acetyl derivative crystallised from ethyl alcohol in colourless needles, m. p. 186—187° (Reverdin and Crépieux, *loc. cit.*, give m. p. 186·5°).

4-*Nitro*-4′-*methoxy*-1 : 1′-*azonaphthalene*.—(a) *Preparation.* 4-Nitro-1-naphthylamine (5 g.) was diazotised in glacial acetic–sulphuric acid by the method of Hodgson and Walker (*J.*, 1933, 1620), and the excess of nitrous acid removed by urea from the solution, which was then stirred into a solution of 1-methoxynaphthalene (4·2 g.) in glacial acetic acid (24 c.c.), and the mixture kept for 7 days, by which time most of the coupled product had separated (7·5 g.). This 4-*nitro*-4′-*methoxy*-1 : 1′-*azonaphthalene* was crystallised twice from glacial acetic acid, and then several times from ethyl alcohol–benzene, whence it was obtained in thick red needles with a metallic lustre, m. p. 224·5° (Found: N, 12·0. $C_{21}H_{15}O_3N_3$ requires N, 11·8%). When diluted with a little water, the residual acetic acid solution gave a precipitate which crystallised from benzene in reddish-brown plates, m. p. 256—259° (Found: N, 12·1%), which must be the isomeric 4-*nitro*-1′-*methoxy*-1 : 2′-*azonaphthalene*.

(b) *Reduction.* The azo-compound (1 g.) was reduced in glacial acetic acid solution with stannous chloride and hydrochloric acid as described above; no hydrochloride separated on keeping, and the white precipitate (0·45 g.) of 3-*nitro*-6-*methoxy*-1 : 2 : 7 : 8-*dibenzocarbazole*, obtained when the solution was poured into water, crystallised from acetic acid in small slightly yellowish plates, m. p. 258—259° (Found: N, 8·4. $C_{21}H_{14}O_3N_2$ requires N, 8·2%), which would neither diazotise nor form a hydrochloride. Alternatively, the azo-compound (1 g.) was dissolved in ethyl alcohol (170 c.c.), sodium hydroxide added (1·5 g.) (the red solution then became blue), and the mixture stirred at 65° with zinc dust (7 g.). The colour rapidly disappeared and the cooled mixture was filtered after the addition of water (50 c.c.), the residue being then extracted with hot benzene. From the cooled extract silvery flakes of the above dibenzocarbazole were obtained which crystallised from benzene (charcoal) in colourless plates having a silvery lustre, m. p. and mixed m. p. with previous preparation, 258—259° (Found: N, 8·5%). When the azo-compound was reduced with stannous chloride and hydrochloric acid as for 4 : 4′-dinitro-1 : 1′-azonaphthalene (above), 3-*amino*-6-*methoxy*-1 : 2 : 7 : 8-*dibenzocarbazole hydrochloride* (1·8 g.) was obtained (Found: Cl, 9·9. $C_{21}H_{16}ON_2$,HCl requires Cl, 10·2%), but attempts to isolate the free base were unsuccessful owing to the rapidity with which oxidation followed basification.

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TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, May 9th*, 1946.]

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16. *Strychnine and Brucine. Part XLVI. The Preparation of* neo*Strychnine and* neo*Brucine.*

By R. N. CHAKRAVARTI and SIR ROBERT ROBINSON.

Strychnine and brucine are converted into the respective *neo*-isomerides by treatment with Raney nickel in boiling xylene. The process provides a convenient method of preparation of the bases and indicates that the isomeric change is essentially a dehydrogenation–hydrogenation.

WHEN methylstrychnine or strychnine methosulphate is heated with methanolic sodium methoxide, or methanol and sodium amalgam, it is converted into methoxymethyldihydro-*neo*strychnine. Reconstitution of the quaternary salt with elimination of methanol occurs under the influence of hot 20% sulphuric acid and, after conversion into the methochloride by way of the methiodide, careful pyrolysis affords *neo*strychnine. The methiodide of this base

is identical with the salt obtained as already mentioned and is convertible to methoxymethyldihydro*neo*strychnine in the same way as strychnine methosulphate (Part XVI, Achmatowicz, Clemo, Perkin, and Robinson, *J.*, **1932**, 767).

These changes paralleled earlier observations in the strychnidine series and, since *neo*strychnidine and *neo*strychnine can be reduced to dihydrostrychnidine-A and dihydrostrychnine respectively, it was clear that the conversion into the *neo*isomerides involved no change in the carbon–nitrogen–oxygen skeleton, but only a new position of the double bond. Furthermore, the unsaturation of the methoxymethyldihydro-bases is already in this new position.

As the shift occurred under the influence of a strong base, the usual migration to an adjacent position was postulated. In Part XLII, however, it has been indicated that *neo*strychnine contains the group :C=C̈–N(b): and therefore the ethylene linkage of strychnine moves at least two steps in the formation of *neo*strychnine. There is no sign of the formation of intermediate products and hence we came to regard the transformation as a dehydrogenation–hydrogenation. It is perhaps analogous to that which occurs when oleic acid is heated with potassium hydroxide and palmitic acid is formed. In one sense the idea is a truism because all shifts of double bonds are necessarily oxidation–reduction processes.

From this point of view the interesting observation of Kotake and Yokohama (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, **1937**, **31**, 321) that strychnine is convertible into *neo*strychnine by heating with selenium, is readily understood. Consideration of the mechanism of the reaction suggested the probable formation of dehydrostrychnine and hydrogen selenide, followed by reduction of the former by the latter. The method is more convenient than the indirect one mentioned above, but it is not so satisfactory as the new process described in the present communication.

It occurred to us that a cleaner preparation might be based on the use of a hydrogenating catalyst. It was found that strychnine and brucine could be converted into the *neo*-bases by refluxing their xylene solutions with Raney nickel; the yields were almost theoretical and about 85% was readily obtained in a pure condition. *neo*Strychnine and *neo*brucine are now very readily accessible and a comprehensive study of their properties and transformations is in progress.

Experimental.

neo*Strychnine*.—Under the conditions of Kotake and Yokohama (*loc. cit.*) the yield of *neo*strychnine obtained by heating strychnine with selenium was found to be 15%. Using a quarter of the prescribed amount of selenium and a lower temperature the yield was increased to 50%.

Strychnine (50 g.) and selenium (25 g.) were powdered together and the mixture was heated at 260° until it melted, and then at 235° for an hour. The product was worked up as described by the Japanese chemists and gave 24 g., m. p. 228°.

In our first experiment with Raney nickel (prepared according to *Org. Synth.*, **21**, 15), 90% alcohol was used as solvent and although some conversion occurred at the boiling point, and *neo*strychnine could be isolated, other products were formed, purification was difficult, and the yield was unfavourable.

Raney nickel (about 1 c.c. of the sediment stored under alcohol) was thoroughly washed with dry xylene, drained, and dry xylene (400 c.c.) and powdered strychnine (50 g.) added. The whole was refluxed for 20 hours; the strychnine disappeared in 5—6 hours and the process is probably completed after 10 hours, but the longer period is advisable as contamination with strychnine hinders the purification of the product. The hot filtered solution deposited *neo*strychnine mixed with a little finely divided nickel; the solid was dissolved in chloroform, filtered through a fine paper, and the solution mixed with an equal volume of ether. Pure *neo*strychnine crystallised in transparent hexagonal plates, m. p. 228° (43 g.), and about 4—5 g. of less pure material could be obtained from the xylene mother liquors.

Success depends on the use of fresh Raney nickel and the exclusion of water and alcohol.

The *neo*strychnine crystallised from alcohol in glistening hexagonal plates or from aqueous alcohol in long needles. The m. p. was not depressed by mixture with a specimen obtained by the selenium process. For confirmation of identity it was converted into the *N*-oxide (Part XVI, *loc. cit.*), m. p. 179—180°, and by the action of methyl iodide in hot acetone into the methiodide, m. p. 325° in agreement with Part XVI (Kotake and Yokohama, *loc. cit.*, give m. p. 315°). The characteristic reaction with *p*-nitrobenzenediazonium chloride described in Part XLII was observed and this affords a distinction from strychnine that could doubtless be developed into a method of analysis of mixtures. We are unable to confirm the statement of Kotake and Yokohama (*loc. cit.*) that *neo*strychnine is changed by 6N-hydrochloric acid. The base dissolves in N-hydrochloric acid but the hydrochloride rapidly crystallises from the solution. Many experiments on the action of hydrochloric acid, dilute and concentrated, hot and cold, on the base left it unchanged. It was also recovered after treatment with boiling dilute acetic acid, glacial acetic acid, alone or mixed with pyridine, and boiling *iso*amyl alcohol containing a little acetic acid. It exhibits therefore no tendency to hydrolyse at the C=C–N group, or to undergo the theoretically possible transformation to dihydro-*ψ*-strychnine, or a derivative thereof.

Action of Perbenzoic Acid on neo*Strychnine*.—The result of this experiment exemplifies the general proposition that the double bond in *neo*strychnine is far less reactive than that in methoxymethyldihydro*neo*strychnine. The latter is converted by perbenzoic acid into methoxymethyl*chano*dihydro-

strychnone by addition of two oxygen atoms (Briggs and Robinson, *J.*, 1934, 590) but *neo*strychnine gives only the *benzoate* of its *N*-oxide.

A solution of *neo*strychnine (3·34 g.) in pure dioxan (100 c.c.) was treated at 35—40° with a solution of perbenzoic acid (cf. Kötz and Steche, *J. pr. Chem.*, 1927, **107**, 203; Lewin, *ibid.*, 1930, **127**, 81) in ether (80 c.c.). After 5 minutes the product separated as snow-white crystals which were collected, washed with ether, and dried (3·62 g.). The substance is soluble in chloroform and dilute aqueous sodium hydroxide, but is insoluble in dilute acids. It crystallises from water in colourless plates, m. p. 183—184° (Found in material dried in a vacuum at the room temperature: C, 69·3, 69·9, 69·6; H, 5·9, 5·9, 6·0; N, 5·9. $C_{21}H_{22}O_3N_2,C_6H_5{\cdot}CO_2H,\frac{1}{2}H_2O$ requires C, 69·8; H, 6·0; N, 5·8%). The substance loses benzoic acid on heating and hence the content of water could not be determined in this way. It is retained after crystallisation from chloroform–ether. This salt can be obtained by mixing hot aqueous solutions of *neo*strychnine *N*-oxide and benzoic acid (1 mole), and on treatment with sulphurous acid it is reduced to *neo*strychnine. The action of perbenzoic acid on strychnine itself was found by Kotake and Mitsuwa (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1937, **31**, 217) to be similar. The product was a benzoate of the *N*-oxide, $C_{21}H_{22}O_3N_2,C_6H_5{\cdot}CO_2H,H_2O$, a substance earlier made from its components by Polonovski and Polonovski (*Bull. Soc. chim.*, 1926, **39**, 1165), whose memoir was not cited by Kotake and Mitsuwa.

neo*Brucine*.—A mixture of powdered brucine (50 g.), Raney nickel (1 c.c. of the alcohol-moist sediment), and xylene (300 c.c.) was distilled. After 15 c.c. had been collected, boiling was continued under reflux for 12 hours. The base was isolated exactly as described for *neo*strychnine and 42 g. of transparent prismatic needles, m. p. 227°, obtained after crystallisation from chloroform–ether (Found: C, 69·7, 69·7; H, 6·6, 6·5. Calc. for $C_{23}H_{26}O_4N_2$: C, 70·0; H, 6·6%). A further few g. could be obtained by concentration of the xylene mother liquor. Addition of *p*-nitrobenzenediazonium chloride to an acid solution gave a yellow precipitate.

The *methosulphate* was prepared from the base (4 g.) and methyl sulphate (1·6 c.c.) in warm methanol (10 c.c.). It crystallised from the cold solution and was recrystallised from water and obtained as colourless, well-defined needles, and from methanol as glistening leaflets, m. p. 252° (decomp.) (Found in material dried at 130°: C, 57·0, 57·3; H, 6·3, 6·3. $C_{23}H_{26}O_4N_2,Me_2SO_4$ requires C, 57·6; H, 6·1%). Double decomposition with sodium iodide gave the methiodide, m. p. 305° (decomp.) [Achmatowicz, Perkin, and Robinson, *J.*, 1932, 775, give m. p. 302—306° (decomp.) and m. p. 225—226° for *neo*brucine], which was also obtained directly from *neo*brucine and methyl iodide.

This methiodide afforded methoxymethyldihydro*neo*brucine, m. p. 205°, when it was treated with methanolic sodium methoxide as described by Achmatowicz, Perkin, and Robinson for methylbrucine; the m. p. 204—205° was given by these authors. As the yield from methylbrucine was only 15% and this substance was previously the only source of *neo*brucine, the advantage of the new method is clear.

*Benzylidene*neo*brucine*.—Potassium hydroxide (0·2 g.) in water (1 c.c.) was added to a boiling solution of *neo*brucine (1 g.) and benzaldehyde (1 c.c.) in alcohol (10 c.c.). The clear orange solution was concentrated somewhat under diminished pressure and diluted with water. The flocculent precipitate was collected and crystallised from methanol; canary yellow, silky needles of the *compound* were thus obtained, m. p. 211° (decomp.) (Found: C, 74·2, 74·4; H, 6·3, 6·3. $C_{30}H_{30}O_4N_2$ requires C, 74·6; H, 6·2%).

neo*Brucine* N-*Oxide*.—*neo*Brucine (2 g.) was heated on the steam-bath with hydrogen peroxide (20 c.c. of 6%) with occasional shaking; a clear solution was obtained in an hour. The filtered solution was concentrated under diminished pressure; the *N-oxide* then crystallised. It separated from water in glistening plates, m. p. 168°, which lost solvent of crystallisation at 100° (Found: loss at 130°, 8·6, 7·7. $C_{23}H_{26}O_5N_2,2H_2O$ requires H_2O, 8·1%). The anhydrous *base*, m. p. 222° (decomp.), is hygroscopic and is also obtained as glistening plates, m. p. 222° (decomp.), by crystallisation from methanol (Found in material dried at 130° with little loss: C, 67·4; H, 6·1. $C_{23}H_{26}O_5N_2$ requires C, 67·3; H, 6·3%). The *N*-oxide is reduced to *neo*brucine by hot aqueous sulphurous acid. It gives the brucine–nitric acid reaction.

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DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, May 14th*, 1946.]

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17. *The Tetrazotisation of* 1 : 5- *and* 1 : 8-*Naphthylenediamines and the Tetranitration of* 1 : 5- *and* 1 : 8-*Di*-p-*toluenesulphonamidonaphthalenes.*

By HERBERT H. HODGSON and JOHN S. WHITEHURST.

1 : 8-Naphthylenediamine is tetrazotised completely by the nitrosylsulphuric–glacial acetic acid method. 1 : 5- and 1 : 8-Di-*p*-toluenesulphonamidonaphthalenes are readily tetranitrated by nitric acid in acetic acid solution.

WHEREAS the tetrazotisation of 1 : 5-naphthylenediamine proceeds normally by the direct method, the process referred to in Beilstein XIII, p. 205, where sodium nitrite in concentrated hydrochloric acid is employed, is most unsatisfactory. The nitrosylsulphuric–glacial acetic acid method of Hodgson and Walker (*J.*, 1933, 1620), however, efficiently tetrazotised 1 : 8-naphthylenediamine as shown by the subsequent Sandmeyer reactions which afforded satisfactory yields of 1 : 8-dichloro-, 1 : 8-dibromo-, and 1 : 8-di-iodo-naphthalenes.

The remarkable facilitation of dinitration by the toluenesulphonamido-group (cf. Bell, *J.*, 1928, 2771; 1931, 2338; Hodgson and Walker, *J.*, 1934, 180) is further exemplified and amplified in the di-*p*-toluenesulphonyl derivatives of 1 : 5- and 1 : 8-naphthylenediamines, which are readily tetranitrated in nitric acid–glacial acetic acid solution. The ease of tetranitration is noteworthy and is the first example of its kind. The resulting tetranitro-compounds are readily hydrolysed by concentrated sulphuric acid to 2 : 4 : 6 : 8-*tetranitro*-1 : 5- and 2 : 4 : 5 : 7-*tetranitro*-1 : 8-*naphthylenediamines*.

The 1 : 5- and 1 : 8-dihalogeno-compounds mentioned in the experimental part have been prepared for the first time from the diamines, with the exception of 1 : 8-dichloronaphthalene, for which the recorded method of preparation in Beilstein (*loc. cit.*) is very unsatisfactory.

Experimental.

Tetrazotisation of 1 : 5-*Naphthylenediamine*.—A partial suspension of the diamine (6 g.) in sulphuric acid (10 c.c., *d* 1·84) and water (150 c.c.) was treated at 0° with one of sodium nitrite (6 g.) in water (50 c.c.), and after complete tetrazotisation had taken place urea (1 g.) was added to remove excess of nitrous acid. The filtered solution was divided into three equal parts which were added severally to solutions of (*a*) cuprous chloride (5 g.) in hydrochloric acid (150 c.c., *d* 1·18), (*b*) cuprous bromide (5 g.) in hydrobromic acid (75 c.c., *d* 1·7) and water (75 c.c.), and (*c*) potassium iodide (10 g.) in water (100 c.c.). The products isolated were from (*a*) 1 : 5-dichloronaphthalene (1·8 g.), from (*b*) 1 : 5-dibromonaphthalene (1·8 g.), and from (*c*) 1 : 5-*di-iodonaphthalene* (2·4 g.), which crystallised from glacial acetic acid in pale fawn needles, m. p. 147° (Found : I, 67·0. $C_{10}H_6I_2$ requires I, 66·8%).

Tetrazotisation of 1 : 8-*Naphthylenediamine*.—A solution of the diamine (6 g.) in glacial acetic acid (50 c.c.) was stirred at 0° into a solution of sodium nitrite (6 g.) in sulphuric acid (50 c.c., *d* 1·84). After 1 hour the mixture was poured into water (50 c.c.) and mixed with chopped ice (50 g.), and urea (1 g.) was added to remove excess of nitrous acid. The solution was filtered, divided into three equal parts, and treated exactly as for tetrazotised 1 : 5-naphthylenediamine. From (*a*), (*b*), and (*c*) were obtained 1 : 8-dichloronaphthalene (1 g.), 1 : 8-dibromonaphthalene (1·5 g.), and 1 : 8-di-iodonaphthalene (1·8 g.) respectively.

Coupling of Tetrazotised 1 : 5-*Naphthylenediamine*.—The diamine (4 g.) was tetrazotised as above, and the solution after neutralisation with calcium carbonate and filtration was divided into 2 equal parts, which were stirred respectively into (*a*) a solution of β-naphthol (4 g.) in water (100 c.c.) containing sodium hydroxide (3 g.), and (*b*) a solution of β-naphthylamine (4 g.) in ethyl alcohol (100 c.c.) and pyridine (50 c.c.) to which sodium acetate (2 g.) in water (20 c.c.) was subsequently added. From (*a*), 1 : 5-*naphthalenebisazo-β-naphthol* separated in almost quantitative yield and crystallised from nitrobenzene in dark red needles, m. p. > 300° (Found : N, 12·3. $C_{30}H_{20}O_2N_4$ requires N, 12·0%), which gave a deep blue colour with concentrated sulphuric acid; from (*b*), 1 : 5-*naphthalenebisazo-β-naphthylamine* was precipitated in almost quantitative amount and crystallised from nitrobenzene in scarlet plates with a green fluorescence, m. p. 284° (Found : N, 18·4. $C_{30}H_{22}N_6$ requires N, 18·0%), which gave a brilliant dark green colour with concentrated sulphuric acid.

Nitration of 1 : 5-*Di*-m-*nitrobenzenesulphonamido- and* 1 : 5-*Di*-p-*toluenesulphonamido-naphthalene*.—The sulphonamide (10 g.) in glacial acetic acid (100 c.c.) was treated dropwise below 45° with a solution of nitric acid (6·5 g., *d* 1·42; 20% excess) in glacial acetic acid (10 c.c.) containing sodium nitrite (0·1 g.). An induction period of *ca.* 2—10 minutes was observed, when the sodium nitrite was omitted, before crystallisation of the tetranitrated products from the solution began; the product was separated (yield *ca.* 8 g.) and then recrystallised from solution in pyridine by careful addition of water. The 2 : 4 : 6 : 8-*tetranitro*-1 : 5-*di*-m-*nitrobenzenesulphonamide* separated from aqueous pyridine in yellow needles, m. p. 263° (decomp.; darkened at 250°) (Found : N, 16·1. $C_{22}H_{12}O_{16}N_8S_2$ requires N, 15·8%). The 2 : 4 : 6 : 8-*tetranitro*-1 : 5-*di*-p-*toluenesulphonamide* separated in yellow needles from aqueous pyridine or better from glacial acetic acid in which it is only moderately soluble, m. p. 257° (decomp.; darkened at 224°) (Found : N, 13·3. $C_{24}H_{16}O_{12}N_6S_2$ requires N, 13·0%).

Nitration of 1 : 8-*Di*-p-*toluenesulphonamidonaphthalene*.—The sulphonamide (10 g.) in glacial acetic acid (50 c.c.) was cautiously nitrated by the dropwise addition of nitric acid (6·5 c.c., *d* 1·42) in glacial acetic acid (6·5 c.c.) containing sodium nitrite (0·1 g.) below 45°. The nitration mixture was kept cool externally by ice for 2 hours, after which the separated 2 : 4 : 5 : 7-*tetranitro*-1 : 8-*di*-p-*toluenesulphonamide* (7·5 g.) was removed and dried; it crystallised from glacial acetic acid, in which it is very soluble, in large yellow rhombs, m. p. 194° (decomp.) (Found : N, 13·3. $C_{24}H_{16}O_{12}N_6S_2$ requires N, 13·0%).

The above tetranitro-1 : 5- and -1 : 8-di-*p*-toluenesulphonamides were readily hydrolysed by intimate admixture with sulphuric acid (100 c.c., *d* 1·84) at 20° and subsequent heating in the water-bath at 45° for 1 hour, after which the mixture was poured on ice and the precipitate of the tetranitronaphthylenediamine removed and dried. 2 : 4 : 6 : 8-*Tetranitro*-1 : 5-*naphthylenediamine* crystallised from nitrobenzene in red plates and from phenol in red pyramids, m. p. 295° (with explosive decomp.) (Found : N, 25·2. $C_{10}H_4O_8N_6$ requires N, 24·85%). 2 : 4 : 5 : 7-*Tetranitro*-1 : 8-*naphthylenediamine* crystallised from nitrobenzene in orange plates, m. p. 260° (decomp.) (Found : N, 25·2%). 4 : 6 : 7 : 9-*Tetranitrodimethyldihydroperimidine* separated from acetone in orange-yellow plates, m. p. 280° (decomp.) (Found : N, 22·5. $C_{13}H_{10}O_8N_6$ requires N, 22·2%).

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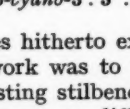
18. *The Search for Chemotherapeutic Amidines. Part IV. Two Polyamidines.*

By H. J. Barber and R. Slack.

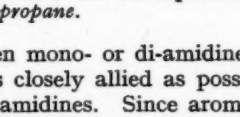
Tetrakis-p-*amidinophenylethylene* has been prepared from the corresponding cyanide. Attempts to prepare tetra-amidinodiphenoxypropane from the corresponding tetracyanide yielded only 5-*cyano*-3 : 3′ : 5′-*triamidino*-αγ-*diphenoxypropane*.

All the amidines hitherto examined by us have been mono- or di-amidines, and the object of the present work was to prepare polyamidines as closely allied as possible to the therapeutically interesting stilbene or diphenoxyalkane diamidines. Since aromatic cyano-groups with an *o*-substituent are difficult to convert into amidines, the choice of compound is limited to 3 : 5 : 3′ : 5′-tetracyanodiphenoxyalkanes or the corresponding stilbenes. The synthesis of the latter class presented extreme difficulties and was rejected in view of the unfavourable indications with the more accessible products. For the former series, 3 : 5-dicyanophenol was the most useful intermediate, since it could yield many of the polycyanides corresponding to the dicyanides successfully employed in these laboratories for preparing the therapeutically active diamidines.

3 : 5-*Dicyanoaniline* (I) was readily obtained from methyl 3 : 5-dinitrobenzoate *via* the 5-nitro-3-aminobenzoate, the 5-*nitro*-3-*cyanobenzoate*, and 3-*nitro*-5-*cyanobenzamide*, and 1-nitro-3 : 5-dicyanobenzene, but attempts to convert it into 3 : 5-dicyanophenol were frustrated by simultaneous hydrolysis of the cyano-groups. The non-volatility of the phenol in steam precluded the use of the procedure advocated by Hodgson (*J. Amer. Chem. Soc.*, 1940, **62**, 230).



(I.)

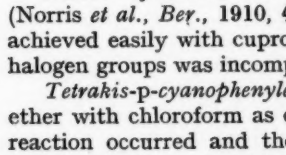


(II).

An alternative route to the *tetracyanide* (II) was successfully accomplished. 3 : 5-Dibromoaniline, prepared from *p*-nitroaniline by dibromination, elimination of the amino-group, and reduction of the nitro-group, was converted into the corresponding phenol which gave 3 : 5 : 3′ : 5′-*tetrabromo*-αγ-*diphenoxypropane* with trimethylene dibromide in alcoholic potash. The tetracyanide (II) was obtained in the usual manner by using cuprous cyanide.

This tetracyanide failed to yield a tetraiminoether, reaction ceasing at the *tri-iminoether* stage. This surprising result suggests a substituent ortho- to one of the cyano-groups. This could arise from a Claisen-type rearrangement during the conversion of the tetrabromo-compound into the tetracyanide (II), but no phenolic properties could be detected in the latter. Migration of the cyano-group has been reported in replacement of $-SO_3H$ by $-CN$ in the naphthalene series (King and Wright, *J.*, 1939, 253), but similar behaviour in the present series is most unlikely, the most probable reason for incomplete reaction being the insolubility of the tri-iminoether hydrochloride.

Tetra-*p*-amidinotetraphenylethylene [III, $R = R_1 = R_2 = R_3 = C(:NH)\cdot NH_2$] can be considered as a substituted diamidinostilbene and might be expected to possess some trypanocidal activity, although in the alkylstilbene diamidine series the activity decreases in ascending the homologous series (Barber and Slack, *J.*, 1944, 612); of interest, too, was the effect on toxicity arising from four amidine groups in the same molecule.



(III.)

Direct cyanation of tetrakis-*p*-bromophenylethylene (III; $R = R_1 = R_2 = R_3 = Br$) (Norris *et al.*, *Ber.*, 1910, **43**, 2940; *J. Amer. Chem. Soc.*, 1916, **38**, 702; 1909, **42**, 2805) was achieved easily with cuprous cyanide in boiling quinoline, but in pyridine replacement of the halogen groups was incomplete.

Tetrakis-p-*cyanophenylethylene* was incompletely converted into the corresponding iminoether with chloroform as diluent, but with a large excess of absolute alcohol alone, complete reaction occurred and the pure *iminoether base* was isolated. Treatment with ammonium isethionate for a considerably longer time than is usually necessary for diamidines gave *tetrakis*-p-*amidinophenylethylene tetraisethionate*.

Both the tri- and the tetra-amidine described above were devoid of trypanocidal activity

when tested against *T. equiperdum* infection in mice, and, compared with the aromatic diamidines, *e.g.*, diamidinostilbene or diamidinodiphenoxypropane, showed a considerably enhanced toxicity due, presumably, to the increased number of amidine groups.

Experimental.

Methyl 5-nitro-3-aminobenzoate was obtained by semi-reduction of methyl 3 : 5-dinitrobenzoate (Cohen and McCandlish, *J.*, 1905, **87**, 1266).

Methyl 5-Nitro-3-cyanobenzoate.—Methyl 5-nitro-3-aminobenzoate (53 g.) was finely powdered, suspended in a mixture of hydrochloric acid (80 c.c., *d* 1·16) and ice (*ca.* 200 g.), and diazotised at 0—10° with sodium nitrite (19 g.) in water (100 c.c.). After being stirred for ½ hour, the diazo-solution was filtered from a little flocculent material and run during 1 hour into a well-stirred mixture of potassium cuprocyanide solution (CuCN, 25 g.; KCN, 37 g.; water, 150 c.c.) and benzene (200 c.c.) at 5—10°. The whole was kept for 1 hour at 60—70°, filtered, and the benzene separated. The solid and the aqueous layer were each washed with more benzene, and the combined benzene extracts washed successively with dilute sodium hydroxide solution and water before removal of the benzene. The residual crude solid was distilled (b. p. 148—155°/2 mm.) or vacuum-sublimed before being crystallised from ethyl alcohol (*ca.* 15 c.c./g.). Yield 45—50%; m. p. 137—138° (Found : N, 13·8. $C_9H_6O_4N_2$ requires N, 13·6%).

5-Nitro-3-cyanobenzamide.—The powdered *ester* was kept with occasional shaking for several days in a stoppered flask with saturated ethyl-alcoholic ammonia (7 c.c./1 g.). It gradually dissolved and the *amide* slowly crystallised. Yield 75—80%. Recrystallisation from acetic acid gave prisms, m. p. 188—189° (Found : N, 21·6. $C_8H_5O_3N_3$ requires N, 22·0%).

1-Nitro-3 : 5-dicyanobenzene.—The amide (8 g.) was boiled under reflux in dry xylene (100 c.c.) with phosphoric oxide (10 g.) for 5 hours. The clear xylene solution was decanted from the sticky pentoxide mass, and the dicyanide crystallised in pure condition. A further crop was obtained on concentrating the xylene. Yield 70—75%; m. p. 205° (Bennett and Wain, *J.*, 1936, 1108, give 205°) (Found : N, 24·1. Calc. for $C_8H_3O_2N_3$: N, 24·3%).

3 : 5-Dicyanoaniline (I).—The nitro-compound (5·7 g.) was first converted into a finely divided form by dissolution in glacial acetic acid and precipitation with water, and reduced in alcohol (90 c.c.) with tin (10 g.) and hydrochloric acid (45 c.c., *d* 1·16) overnight at 35—40°. The filtered solution was concentrated, and the crude amine obtained by precipitation with sodium hydroxide. The product was dissolved in hot alcohol, treated with charcoal, filtered, and precipitated with water. After dissolution in 4N-hydrochloric acid, the *amine* was precipitated with ammonia. Yield 50%; m. p. 189—190° (Found : N, 28·6. $C_8H_5N_3$ requires N, 29·4%). Reduction with iron or with Adams's platinum oxide catalyst failed.

3 : 5-Dibromophenol was obtained from 3 : 5-dibromoaniline by using the general conditions given by Hodgson (*loc. cit.*), but as this phenol was only slightly volatile in steam, it was extracted with benzene and distilled in a vacuum; b. p. 120—122°/2—3 mm., m. p. 79—80°; yield 50%.

3 : 5 : 3′ : 5′-Tetrabromo-αγ-diphenoxypropane.—3 : 5-Dibromophenol (30 g.) in ethyl alcohol (50 c.c.) was treated with a solution of potassium hydroxide (6—7 g.) in methanol (50 c.c.) and 1 : 3-dibromopropane (12 g.) and the solution boiled overnight. The *product* which separated, together with potassium bromide, was filtered off and washed with water and was then sufficiently pure for the next stage. Yield 75—80%, m. p. 123—124° (Found : Br, 59·7. $C_{15}H_{12}O_2Br_4$ requires Br, 59·0%).

3 : 5 : 3′ : 5′-Tetracyano-αγ-diphenoxypropane (II).—The tetrabromo-compound (12·0 g.) was mixed with dry cuprous cyanide (9·4 c.c.) and dry pyridine (10 c.c.) and heated in a metal-bath. A little pyridine was distilled out to enable an internal temperature of 200° to be maintained. After 2½ hours the melt was cooled somewhat, diluted with pyridine (12 c.c.), and poured into hydrochloric acid (70 c.c., *d* 1·16) at 50°. The solid was collected, washed with 2N-hydrochloric acid, then with water, and dried. Attempts to purify this failed, probably since some conversion of cyanide to amide had occurred. The crude product was therefore boiled in xylene (100 c.c.) with phosphoric oxide (10 g.) for 2 hours. Recrystallisation from glacial acetic acid gave the pure *compound*, m. p. 188°, in 50% yield (Found : N, 17·4. $C_{19}H_{12}O_2N_4$ requires N, 17·1%).

5-Cyano-3 : 3′ : 5′-triamidino-αγ-diphenoxypropane.—3 : 5 : 3′ : 5′-Tetracyano-αγ-diphenoxypropane (II) (3·3 g.) in dry dioxan (20 c.c.) and ethyl alcohol (5·7 c.c.) was saturated at 0° with hydrogen chloride and kept at room temperature for 7 days. On converting the resulting iminoether into amidine, there was obtained, not the expected 3 : 5 : 3′ : 5′-tetra-amidine, but 5-cyano-3 : 3′ : 5′-triamidino-αγ-diphenoxypropane hydrochloride which crystallised as a *dihydrate* on addition of its concentrated aqueous solution to acetone [Found : N, 18·8; Cl, 20·5; (N : Cl = 2·33 : 1); loss at 100°/1 mm., 5·2. $C_{19}H_{21}O_3N_7,3HCl,2H_2O$ requires N, 18·7; Cl, 20·35; (N : Cl = 2·33 : 1); H_2O, 6·8%].

Repeated attempts to convert 3 : 5 : 3′ : 5′-tetracyano-αγ-diphenoxypropane into the corresponding tetraiminoether were unsuccessful. An ethyl-alcoholic suspension of the tetracyanide, saturated at 0° with hydrogen chloride and kept for 14 days at room temperature, likewise gave, on conversion into amidino-compound, the monocyano-triamidine (Found : N, 18·3%). When the dioxan–ethyl alcohol suspension of the tetracyanide saturated at 0° with hydrogen chloride was kept at room temperature for 19 days and the resulting iminoether isolated as the hydrochloride, it proved to be the *tri-imino-ether hydrochloride* (Found : OEt, 23·2, 23·8. $C_{25}H_{30}O_5N_4,3HCl$ requires OEt, 23·4. $C_{27}H_{36}O_6N_4,4HCl$ requires OEt, 27·4%). The sodamide method of B.P. 538,463 was equally unsuccessful.

Tetrakis-p-cyanophenylethylene.—Tetrakis-*p*-bromophenylethylene (45·0 g.) was intimately mixed with dry cuprous cyanide (38·5 g.), and the mixture fed slowly into quietly boiling quinoline (150 c.c.). After 1 hour's heating under reflux, the mixture was poured into hot concentrated hydrochloric acid (500 c.c.), and the residue collected by filtration while hot, and washed well with water. The crude solid was then dissolved in boiling glacial acetic acid, filtered (charcoal), and precipitated with water. Recrystallisation from glacial acetic acid gave the *tetracyanide* as pale yellow, blunt needles (15·0 g.),

m. p. 346—348°. Further recrystallisation from the same solvent gave the pure compound, m. p. 352—353° (87% return) [Found: N, 12·8; *M* (Rast), 425. $C_{30}H_{16}N_4$ requires N, 13·0%; *M*, 432].

Tetraphenylethylenetetra-p-*iminoethyl Ether*.—The finely ground cyanide (5·0 g.) in dry ethanol (50 c.c.) was saturated with dry hydrogen chloride at 0°. After standing for 3 weeks in a closed tube at room temperature, the crude iminoether hydrochloride was separated by filtration, washed with ether, and converted into the corresponding base by treatment with excess of sodium carbonate solution and chloroform. The chloroform layer was separated, washed till neutral, dried, and the solvent evaporated. Crystallisation of the residue from benzene gave the *iminoether* as colourless needles (3·2 g.), m. p. (decomp.) 225° (Found: C, 73·8; H, 6·5; N, 9·3; OEt, 29·2. $C_{38}H_{40}O_4N_4$ requires C, 74·0; H, 6·48; N, 9·1; OEt, 29·2%).

Tetrakis-p-*amidinophenylethylene*.—The iminoether base (1·0 g.) was heated for 18 hours at 50—60° with aqueous alcohol (3 c.c.; 9 c.c.) containing ammonium isethionate (1·4 g.). The clear solution was evaporated to dryness at 10 mm. (temp. 40°), and the residue treated with acetone and filtered. The solid (1·6 g.) was dissolved in the minimum quantity of water, and the solution filtered (charcoal) and poured slowly with stirring into acetone (100 c.c.) at 0°. The micro-crystalline *amidine isethionate* was filtered off, washed with acetone, and dried in a vacuum (Found: C, 44·8; H, 5·4; N, 11·2. $C_{38}H_{52}O_{16}N_8S_4$ requires C, 45·5; H, 5·2; N, 11·2%).

The authors wish to thank Mr. S. Bance, B.Sc., and the staff of the Microanalytical Department of May and Baker Ltd. for carrying out the semi-microanalyses, Dr. A. J. Ewins, F.R.S., for his interest in this work, and the Directors of May and Baker Ltd. for permission to publish these results.

Research Laboratories, May and Baker Ltd., Dagenham. [*Received, May 6th*, 1946.]

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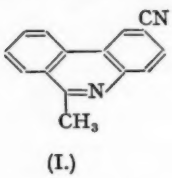
19. *The Search for Chemotherapeutic Amidines. Part V. Phenanthridines.*

By H. J. Barber, (Miss) P. Z. Gregory, F. W. Major, R. Slack, and A. M. Woolman.

3-*Amidino*-9-*methyl*-, 3-*amidino*-9-p-*amidinophenyl*-, *and* 7-*amidino*-9-p-*amidinophenyl*-*phenanthridine*, and the *methochloride* of the last base have been prepared and found to have little trypanocidal activity.

The marked trypanocidal activity found in the phenanthridine series, especially among nuclear quaternised diamines (Walls, *J.*, 1938, 389; 1945, 294), has led us to examine some analogous amidines to see if the therapeutically active amidine group in association with the phenanthridine nucleus gave products having an enhanced trypanocidal action.

As an exploratory experiment, we attempted the preparation of the mono-amidine 3-*amidino*-9-*methylphenanthridine* in order, primarily, to judge the effect of the amidine group on the general toxicity of the nucleus and to see whether any trypanocidal activity could be expected from the mono-amidines of this series.



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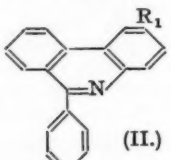

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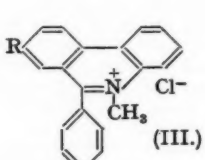

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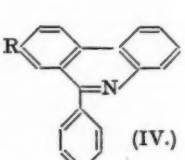

(IV.)

2-Acetamidodiphenyl was brominated in glacial acetic acid to produce 5-bromo-2-acetamidodiphenyl in excellent yield (Scarborough and Waters, *J.*, 1927, 89). Ring closure of this compound with phosphorus oxychloride gave 3-*bromo*-9-*methylphenanthridine*, but smooth cyanation of this product proved difficult. Prior cyanation of the diphenyl was successful, and ring closure by heating with phosphorus oxychloride gave the required 3-*cyano*-9-*methylphenanthridine* (I) in moderate yield. The cyanide was converted *via* the iminoether into the corresponding *amidine dihydrochloride* in the usual way. This compound exhibited little or no trypanocidal activity, and our attention then turned to diamidines of the phenanthridine series.

2-p-*Bromobenzamidodiphenyl* was obtained in satisfactory yield by the interaction of *p*-bromobenzoyl chloride and 2-aminodiphenyl in chlorobenzene. Direct bromination in acetic acid gave 5-*bromo*-2-p-*bromobenzamidodiphenyl*. The longer route involving the stages 2-amino- → 2-acetamido- → 5-bromo-2-acetamido- → 5-bromo-2-amino- → 5-bromo-2-*p*-bromobenzamido-diphenyl gave slightly better yields.

Ring closure of the dibromo-compound was effected in good yield with phosphorus oxychloride in nitrobenzene, the 3-*bromo*-9-p-*bromophenylphenanthridine* (II; R = R_1 = Br) so obtained being converted smoothly into the required *dicyanide* (II; R = R_1 = CN) by treatment with cuprous cyanide in quinoline.

The dicyanide was converted into the *diamidine dihydrochloride* [II; R = R_1 = C(:NH)·NH_2,HCl] through the corresponding iminoether base by treatment with ammonium chloride. The dihydrochloride was very sparingly soluble in water (1% at 23°), and even at this concentration tended to form gels. The amidine exhibited no activity against *T. equiperdum*.

7-Nitro-9-*p*-nitrophenylphenanthridine, prepared by Walls's method (*loc. cit.*), was the starting point for the preparation of the amidines [III and IV; R = R_1 = C(:NH)·NH_2], which are analogues of one of the most active phenanthridinediamines (III; R = R_1 = NH_2). Reduction to 7-amino-9-*p*-aminophenylphenanthridine (IV; R = R_1 = NH_2) was effected by treatment with stannous chloride in glacial acetic acid (cf. Walls, *loc. cit.*), and the required dicyanide (IV; R = R_1 = CN) was obtained from the diamine by means of the Sandmeyer reaction.

The di-iminoether [IV; R = R_1 = C(:NH)·OC_2H_5] was not formed on treating the cyanide in chloroform with absolute alcohol and dry hydrogen chloride, but a reasonable yield was obtained in about ten days when the chloroform was omitted. The final product was isolated as the soluble *amidine trihydrochloride*, the isethionate being deliquescent and the corresponding base gel-like.

This amidine exhibited slight trypanocidal activity against *T. equiperdum* infection in mice, and the corresponding *methochloride* was prepared, the quaternary group being an apparently essential feature for marked activity in the diamine series. As it was not possible directly to quaternise the amidine without affecting the amidine group, the dicyanide (IV; R = R_1 = CN) in nitrobenzene solution was treated with methyl sulphate to give the corresponding *methyl methosulphate*. 7-*Cyano*-9-p-*cyanophenyl*-10-*methylphenanthridinium chloride* was obtained either by direct treatment of an aqueous solution of the methyl methosulphate with ammonium chloride or by the action of silver chloride on the corresponding *bromide*. Both methods gave products with slightly high halogen values, but the excess halogen was loosely combined; the same phenomenon has been noted independently in the quaternised dinitrophenanthridines (Walls, private communication).

Treatment of an aqueous solution of the chloride with picric acid gave the *picrate*, which analysed correctly and contained no halogen. This disposed of any suggestion of nuclear halogenation by migration from the quaternary nitrogen atom.

The cyanide was smoothly converted through the iminoether hydrochloride into 7-*amidino*-9-p-*amidinophenyl*-10-*methylphenanthridinium chloride dihydrochloride* which was heavily hydrated and quite soluble in water. It exhibited no activity against either *T. equiperdum* or *T. congolense* infections.

Experimental.

3-*Bromo*-9-*methylphenanthridine*.—5-Bromo-2-acetamidodiphenyl (5 g.) was boiled gently under reflux with freshly distilled phosphorus oxychloride (10 g.) for 30 mins. After removal of excess oxychloride under reduced pressure, the residue was treated with warm N-hydrochloric acid (100 c.c.), the solution filtered (charcoal), and excess of concentrated hydrochloric acid added. The phenanthridine hydrochloride was collected after cooling the solution, washed with 2N-hydrochloric acid, and treated with ammonia to give the *base* (2·45 g.), m. p. 128—129° (Found: N, 5·2. $C_{14}H_{10}NBr$ requires N, 5·15%).

2-*Acetamido*-5-*cyanodiphenyl*.—5-Bromo-2-acetamidodiphenyl (20 g.) was heated with cuprous cyanide (8·0 g.) and pyridine (8·0 c.c.) at 170—200° for 3 hours. The melt was poured into a solution of potassium cyanide (20 g.) in water (100 c.c.), and the mixture warmed on the steam-bath and allowed to stand for 1 hour. The solid was filtered off and crystallised from alcohol (30 c.c.; charcoal) to give a crude product (10·85 g.) which still contained copper. Further treatment with warm 20% potassium cyanide solution followed by recrystallisation from alcohol gave the pure *cyano*-compound (9·12 g.), m. p. 129—130° (mixed m. p. with bromo-compound 102—104°) (Found: N, 11·8. $C_{15}H_{12}ON_2$ requires N, 11·9%).

3-*Cyano*-9-*methylphenanthridine*.—The acetamidocyano-compound (3·0 g.) and phosphorus oxychloride (7·5 g.) were boiled gently under reflux for 30 mins. Removal of the oxychloride gave a gum which was kept in contact with water overnight. Solution in pyridine (50 c.c.) followed by precipitation with 0·5N-sodium hydroxide solution (300 c.c.) gave a granular precipitate which was filtered off, washed, dried, and sublimed at 0·5 mm. to give the crude *phenanthridine* (0·85 g., 31%). Recrystallisation from alcohol (75 c.c.) gave the pure compound (0·62 g.), m. p. 202—203·5° (Found: N, 12·8. $C_{15}H_{10}N_2$ requires N, 12·85%). The yield of crude material could probably be improved by the use of nitrobenzene in the reaction mixture as in the later experiments of this series (cf. Walls, *loc. cit.*, and B.P. 520,273).

The same product was obtained by treatment of 3-bromo-9-methylphenanthridine with cuprous cyanide in pyridine, but it could not be freed from halogen.

3-*Amidino*-9-*methylphenanthridine*.—3-Cyano-9-methylphenanthridine (2·5 g.) was dissolved in dry chloroform (75 c.c.) and dry alcohol (1·8 c.c.). After saturation with dry hydrogen chloride at 0°, the mixture was kept at 15° for 16 days. The solid was filtered off, washed with chloroform and ether, and dried in a vacuum to give the crude iminoether hydrochloride (3·57 g.). Treatment with concentrated alcoholic ammonia (75 c.c.), and crystallisation of the residue from hot water (175 c.c.) by addition of excess concentrated hydrochloric acid, gave the *amidine dihydrochloride* (3·05 g.) as fine needles. Drying of this heavily hydrated form was effected by boiling with dry alcohol, the dihydrate then being formed (Found: N, 12·2; Cl, 19·9. $C_{15}H_{13}N_3,2HCl,2H_2O$ requires N, 12·2; Cl, 20·7%).

2-p-*Bromobenzamidodiphenyl*.—2-Aminodiphenyl (17·0 g.) was dissolved with *p*-bromobenzoyl chloride (24·0 g.) in dry chlorobenzene (150 c.c.) and heated under reflux for 1 hour. A clear solution rapidly formed and evolution of hydrogen chloride was complete after about 45 mins. The solution was filtered while still hot (charcoal) and 50 c.c. of chlorobenzene were removed by distillation. On slow cooling (rapid cooling produced gels) stellate clusters of the crude product separated (21·3 g.; 61%). Addition of light petroleum to the filtrate gave a further crop (9·2 g.; 26%). Recrystallisation from light petroleum (b. p. 80—100°) gave the pure *amide*, m. p. 128—129°, in colourless needles (Found: N, 4·0; Br, 22·6. $C_{19}H_{14}ONBr$ requires N, 3·98; Br, 22·7%).

5-*Bromo*-2-p-*bromobenzamidodiphenyl*.—5-Bromo-2-aminodiphenyl (12·5 g.) (Scarborough and Waters, *loc. cit.*) in pyridine (20 c.c.) was treated with *p*-bromobenzoyl chloride (11 g.) and warmed to complete solution. After standing overnight the whole was poured into excess of ice-cold dilute hydrochloric acid, and the solid filtered off, washed, and recrystallised from alcohol to give the *dibromo*-compound, m. p. 161° (16·5 g.). The same product was obtained in 80% yield (pure) by aroylation in boiling chlorobenzene solution and in 71% yield by direct bromination of *p*-bromobenzamidodiphenyl under conditions similar to those used for bromination of the acetamido-compound (Found: N, 3·3. $C_{19}H_{13}ONBr_2$ requires N, 3·25%).

3-*Bromo*-9-p-*bromophenylphenanthridine*.—The above amide (15 g.) in nitrobenzene (50 c.c.) and phosphorus oxychloride (15 c.c.) were heated under reflux for 2 hours. Treatment with ice and water, followed by removal of the nitrobenzene in steam, gave a quantitative yield of the *phenanthridine*, m. p., after crystallisation from alcohol, 234—235°. Omission of the nitrobenzene led to a decreased yield of material (Found: N, 3·6; Br, 38·2. $C_{19}H_{11}NBr_2$ requires N, 3·4; Br, 38·7%).

3-*Cyano*-9-p-*cyanophenylphenanthridine*.—The foregoing dibromo-compound (10 g.) and cuprous cyanide (4·35 g.) were intimately mixed and fed slowly (15 mins.) into boiling quinoline (40 c.c.). Refluxing was then continued for 30 mins., and the mixture was then cooled, treated with dilute hydrochloric acid, and the solid filtered off, washed, and dried. Sublimation at 280—320°/2 mm. gave a crude product (5·8 g.) which recrystallised from pyridine or nitrobenzene to give the pure *cyanide* (3·5 g.), m. p. 340° (Found: N, 13·4. $C_{21}H_{11}N_3$ requires N, 13·75%).

3-*Amidino*-9-p-*amidinophenylphenanthridine*.—The dicyanide (5 g.) was finely ground (200 mesh) and suspended in dry chloroform (100 c.c.) and dry alcohol (5 c.c.). Saturation with dry hydrogen chloride was carried out at 0°, and after standing for 8 days the crude iminoether base, m. p. 150—153°, was isolated in the usual manner.

The base (4·9 g.) was dissolved in alcohol (130 c.c.), and a solution of ammonium chloride (1·32 g.) in water (5 c.c.) added. The whole was kept at 70° for 4 hours and deposition of the *amidine dihydrochloride*, which began after 1 hour, was completed by addition of cold acetone. The solid (4·0 g.) was filtered off and dried, but purification was rendered difficult by its tendency towards gel formation with solvents. A solution in hot water rapidly set to a loose gel which was reversed only on boiling, and the forms obtained by precipitation with acetone from methanolic or acidic aqueous solution appeared to be amorphous. Purification was finally effected by careful precipitation of an aqueous gel with acetone. The solubility of the salt was approximately 1% at 23° (Found: N, 15·5; Cl, 15·8. $C_{21}H_{17}N_5,2HCl,2H_2O$ requires N, 15·6; Cl, 15·9%). Only one molecule of water was lost by drying in a vacuum at 100° and as the resulting monohydrate combined with atmospheric moisture during weighing, it was impossible to obtain accurate loss in weight figures.

7-*Amino*-9-p-*aminophenylphenanthridine*.—A solution of stannous chloride (360 g.) in hydrochloric acid (360 c.c., *d* 1·16), heated to about 70°, was added all at once to a boiling suspension of 7-nitro-9-*p*-nitrophenylphenanthridine (50 g.) in glacial acetic acid (350 c.c.). When the vigorous reaction had subsided, the mixture was refluxed for 75 mins. and allowed to cool. The stannichloride was filtered off, dissolved in the least quantity of water, and the ice-cooled solution made alkaline to phenolphthalein with 50% sodium hydroxide. The amine thus liberated was dissolved in a small volume of dioxan, the solution filtered, and the amine reprecipitated by adding a large volume of water; it was collected, washed with water, dried at 100°, and crystallised from *n*-butyl alcohol to give yellow needles, m. p. 208—210° (20·5 g., 50%) (Found: N, 14·5. Calc. for $C_{19}H_{15}N_3$: N, 14·7%).

7-*Cyano*-9-p-*cyanophenylphenanthridine*.—A suspension of the foregoing amine (20 g.) in hydrochloric acid (140 c.c., *d* 1·16) and water (200 c.c.) was cooled in ice and mechanically stirred. Sodium nitrite (10·3 g. in 40 c.c. of water) was added at 0—5°, and the solution then neutralised with sodium carbonate. The diazonium solution was added to potassium cuprocyanide solution (15·7 g. CuCN; 35·2 g. KCN; 210 c.c. H_2O) at 60°, and the resulting mixture heated on the steam-bath for 2 hours. The solid was separated, washed well with water, and dried at 100°. It was then sublimed at 300°/0·1 mm., the *cyanide* being obtained as a pale yellow, crystalline sublimate (6·9 g.). It crystallised from pyridine in pale yellow, matted needles, m. p. 322—323° (4·5 g., 21%) (Found: C, 82·2; H, 3·7; N, 13·4. $C_{21}H_{11}N_3$ requires C, 82·5; H, 3·6; N, 13·8%).

7-*Amidino*-9-p-*amidinophenylphenanthridine*.—The foregoing dicyanide (2 g.) in lime-dried alcohol (15 c.c.) was saturated with hydrogen chloride and left sealed at 0° for 12 days. The iminoether base, m. p. 147—148° (1·53 g., 55%), isolated in the usual manner, was used for the preparation of the amidine without further purification. It (0·86 g., 1 mol.) was heated with ammonium chloride (0·26 g., 2·2 mols.)

in aqueous alcohol (1 c.c., 4 c.c.) at 60—65° for 4 hours. Precipitation with acetone and crystallisation (0·72 g.) from ethyl alcohol gave prismatic needles, m. p. 282° (decomp.) (0·3 g.), which were a mixture of di- and tri-hydrochlorides (Found: N, 14·4; Cl, 19·2%; N : Cl = 5 : 2·6). This solid, on treatment with 4N-hydrochloric acid, was converted into the *trihydrochloride*, m. p. 294—295° (decomp.) (Found: N, 13·8; Cl, 20·8; N : Cl = 5 : 3. $C_{12}H_{17}N_5,3HCl,3H_2O$ requires N, 13·9; Cl, 21·2%).

7-Cyano-9-p-cyanophenyl-10-methylphenanthridinium Chloride.—Methyl sulphate (2·8 c.c.) was added to a solution of 7-cyano-9-*p*-cyanophenylphenanthridine (5 g.) in nitrobenzene (35 c.c.) at 180°. The red solution was kept at 200° for 15 mins., and the nitrobenzene removed by steam-distillation. The resultant aqueous solution (200 c.c.) was filtered hot, and ammonium chloride (45 g.) added to the hot filtrate. The solid which separated was filtered off and crystallised from aqueous methanol (7 c.c.; 70 c.c.). The *chloride* crystallised in pale yellow needles, m. p. 314—315° (decomp.) (2·8 g., 48%) (Found: N, 11·4, 11·0, 11·1; Cl, 10·8, 10·3, 10·3. $C_{22}H_{14}N_3Cl$ requires N, 11·8; Cl, 10·0%).

The *picrate* was prepared from the chloride in aqueous solution, and crystallised twice from acetone to give flat needles, m. p. 218—219° (decomp.) (Found: C, 62·0; H, 2·3; N, 15·2, 15·35. $C_{28}H_{16}O_7N_6$ requires C, 61·5; H, 2·9; N, 15·4%).

The *bromide* was prepared exactly as above, ammonium bromide being substituted for the chloride. The solid which separated was filtered off, washed with a little water, and crystallised from aqueous alcohol (150 c.c.; 100 c.c.) to give the bromide, m. p. 304—306° (decomp.) (3·4 g., 60%) (Found: N, 10·3, 10·4; Br, 21·0, 21·6. $C_{22}H_{14}N_3Br$ requires N, 10·5; Br, 20·0%). It was converted into the above chloride as follows. To silver chloride (prepared from 2·15 g. of nitrate, and well washed by decantation with water and methanol) were added the finely ground bromide (2·15 g.) and methanol (40 c.c.), and the mixture was refluxed for 1 hour, filtered hot, and the filtrate evaporated to dryness in a vacuum to give the chloride (1·7 g., 89%). This solid, together with that from a similar experiment (2·44 g. in all), crystallised from 2N-hydrochloric acid (110 c.c.) in almost colourless needles, m. p. 310—311° (1·84 g., 75% return) (Found: N, 11·1; Cl, 10·3%).

7-Amidino-9-p-amidinophenyl-10-methylphenanthridinium Chloride.—A suspension of 7-cyano-9-*p*-cyanophenyl-10-methylphenanthridinium chloride (0·4 g.) in lime-dried alcohol (7 c.c.) was saturated with dry hydrogen chloride below 0°, and then left at 0° for two weeks. The excess alcohol was then removed in a vacuum at 35—40°, leaving the di-iminoether dihydrochloride as a pale yellow solid.

The *diamidine dihydrochloride*, m. p. 270—272° (decomp.), obtained by treatment of the above hydrochloride with alcoholic ammonia, was washed with acetone and dried in a vacuum (0·36 g., 56%) (Found: N, 12·3; Cl, 18·9; N : Cl = 5·0 : 3·0. $C_{22}H_{20}N_5Cl,2HCl,6H_2O$ requires N, 12·3; Cl, 18·7%).

The authors wish to thank Mr. J. J. Boam, B.Sc., for carrying out some of the preliminary experimental work, Mr. S. Bance, B.Sc., and his staff for the semi-microanalyses, Dr. A. J. Ewins, F.R.S., for his interest, and the Directors of May and Baker Ltd. for permission to publish this work.

RESEARCH LABORATORIES, MAY AND BAKER LTD.,
DAGENHAM, ESSEX.

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20. *The Search for Chemotherapeutic Amidines. Part VI. Pyridines.*

By (MISS) P. Z. GREGORY, S. J. HOLT, and R. SLACK.

Two amidines containing pyridine nuclei, *αε-bis-(5-amidino-2-pyridyloxy)pentane dihydrochloride* and 2-p-*amidinostyrylpyridine*, have been synthesised. Attempts to convert αγ-bis-(5-cyano-2-pyridyloxy)propane into the corresponding diamidine failed.

Two of the most interesting of the therapeutic series of diamidines prepared in these laboratories are 4 : 4′-diamidino-αγ-diphenoxypropane and 4 : 4′-diamidino-αε-diphenoxypentane ("Propamidine" and "Pentamidine"). Both compounds have found use in the treatment of trypanosome infections in man, and the former has also been used as a bacteriostatic agent. The pyridine analogues [I; $n = 3$ or 5, $R = R_1 = C(:NH)\cdot NH_2$] were therefore deemed worthy of preparation.

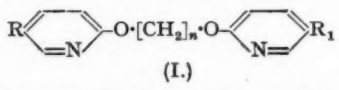
2-Amino-5-cyanopyridine was obtained by a modification of the method of Caldwell (*J. Amer. Chem. Soc.*, 1944, **66**, 1479), *viz.*, by treatment of 5-iodo-2-aminopyridine with cuprous cyanide in pyridine. The required cyanide was not obtained when the solvent was omitted. The cyanide gave the hitherto-unknown *2-hydroxy-5-cyanopyridine* on treatment with sodium nitrite in cooled sulphuric acid. We were unable to condense the hydroxy-compound with αε-dibromopentane, and only small yields of the required cyanide were obtained by treatment of the silver salt of the hydroxypyridine with dibromopentane in dioxan. The use of dry alcohol effected a slight improvement, whereas ethylene glycol as solvent afforded none of the required compound. A startling improvement was accomplished by using specially dried reactants and solvents. The hydroxypyridine (silver salt) and dibromopentane (both dried intensively over phosphoric oxide) gave, in dioxan previously dried by refluxing with sodium for 48 hours, excellent yields of *αε-bis-(5-cyano-2-pyridyloxy)pentane* (I; $n = 5$, $R = R_1 = CN$).

Conversion into the corresponding iminoether occurred satisfactorily in chloroform and

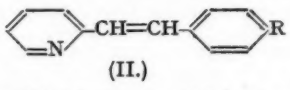
absolute alcohol treated with dry hydrogen chloride. It was found best not to purify the iminoether base, as considerable reconversion into the dicyanide occurred on attempted recrystallisation, a manifestation of the ease with which many iminoether bases decompose into alcohol and cyanide. *αε-Bis-(5-amidino-2-pyridyloxy)pentane dihydrochloride* was obtained by treatment of the iminoether base with ammonium chloride.

Under conditions similar to those used for the pentane derivative, αγ-bis-(5-cyano-2-pyridoxy)propane (I; $n = 3$, $R = R_1 = CN$) was prepared, but in poor yields. All attempts to convert this compound into the corresponding iminoether failed.

Yet another interesting amidine of the carbocyclic series is 4 : 4′-diamidinostilbene (" Stilbamidine "), and we accordingly decided to investigate the analogue [II, $R = C(:NH)\cdot NH_2$],



(I.)



(II.)

in which the pyridine ring might possibly supply the second basic centre which is presumably necessary for trypanocidal activity (see Ashley *et al.*, *J.*, 1942, 103).

p-Cyanobenzaldehyde condensed easily and smoothly with α-picoline in the presence of acetic anhydride (cf. Chiang and Hartung, *J. Org. Chem.*, 1945, **10**, 21) to give 2-p-*cyanostyrylpyridine* (II, R = CN), and the corresponding iminoether was obtained by the usual method. This, on treatment with ammonium chloride, gave **2-*p*-amidinostyrylpyridine**, isolated as its *dihydrochloride*, readily soluble in water. It showed no trypanocidal activity, but the diamidine [I; $n = 5$, $R = R_1 = C(:NH)\cdot NH_2$] exhibited slight activity against *T. equiperdum* in mice. It also inhibited the growth of *Staph. aureus* at a dilution of 1 : 64,000, but even so, this activity is less than half that of the carbocyclic analogue (" Pentamidine ").

Experimental.

2-Amino-5-cyanopyridine.—5-Iodo-2-aminopyridine (11 g.) and dry cuprous cyanide (5 g.) were refluxed for 30 mins. in dry pyridine (12 c.c.). The pyridine was distilled off, and the residue rapidly distilled in a vacuum with a naked flame, using a wide tube receiver and without employing an air leak, the required compound being obtained as a pale yellow solid (4·6 g., 75·5%), m. p. 164°.

2-Hydroxy-5-cyanopyridine.—Sodium nitrite (15·4 g.) was added in small quantities to a well-stirred solution of 2-amino-5-cyanopyridine (15 g.) in sulphuric acid (18·5 c.c., *d* 1·84) and water (180 c.c.) kept at 0—5°. The solution remained clear at first, but evolution of nitrogen soon occurred with the separation of a white solid. The thick suspension was allowed to reach room temperature and was then heated on the steam-bath for 30 mins. The cooled suspension was filtered, and the residue recrystallised (charcoal) from water (400 c.c.), giving the required *compound* (13·1 g., 87·5%), m. p. 259—260° (Found : C, 59·8; H, 3·3; N, 23·1. $C_6H_4ON_2$ requires C, 60·0; H, 3·3; N, 23·3%). To a solution of this compound (1·2 g.) in N-sodium hydroxide (10·0 c.c.) and water (25 c.c.), 0·1N-silver nitrate solution was added, with stirring. The semi-gelatinous suspension was heated on the steam-bath for 30 mins. to complete the reaction, and the silver salt was filtered off and washed well with water and alcohol.

αε-Bis-(5-cyano-2-pyridyloxy)pentane.—The silver salt (11·35 g.) was dried in the steam-oven for 24 hours and over phosphoric oxide in a vacuum for 12 hours, then refluxed for 24 hours in pure dry dioxan (125 c.c.) with 1 : 5-dibromopentane (4·0 c.c.) which had been dried over phosphoric oxide. The suspension was filtered hot, and the filtrate deposited a white solid, which was washed with ether. The filtrate from this was diluted with 5 vols. of water, giving a soft solid; washing with ether removed an oil, and the solid remaining was combined with that obtained above and re-crystallised (charcoal) from alcohol (400 c.c.), giving the required *compound* as a white crystalline powder, m. p. 170—171° (5·4 g., 70%) (Found : C, 66·4; H, 5·3; N, 18·10. $C_{17}H_{16}O_2N_4$ requires C, 66·5; H, 5·2; N, 18·15%).

αε-Bis-(5-amidino-2-pyridyloxy)pentane Dihydrochloride.—The foregoing cyano-compound (1·5 g.) in dry chloroform (40 c.c.) and dry alcohol (1·25 c.c.) was saturated at −10° with dry hydrogen chloride. The tube was securely stoppered and kept at 0° for 13 days. The product was added to excess of sodium carbonate solution at 0°, and the liberated iminoether base extracted with chloroform. The chloroform solution was washed free from alkali with ice-water, dried (sodium sulphate), and the solvent removed under reduced pressure at a low temperature. The residue was dissolved in alcohol (25 c.c.) by warming, and an aqueous solution of ammonium chloride (0·588 g., 2·05 mols.) added. The resulting solution was kept at *ca.* 50° for 12 hours, and the product poured into acetone (300 c.c.). The sticky precipitate hardened to a white solid which was crystallised from alcohol (50 c.c.), giving the required *amidine dihydrochloride* (1·0 g., 50%) (Found : C, 48·2; H, 5·7; N, 19·75; Cl, 16·6. N : Cl = 3·0 : 1. $C_{17}H_{24}O_2N_6Cl_2,\frac{1}{2}H_2O$ requires C, 48·1; H, 5·9; N, 19·8; Cl, 16·7%).

αγ-Bis-(5-cyano-2-pyridyloxy)propane.—Quantities and conditions were as for the corresponding pentane derivative, but dry 1 : 3-dibromopropane (3·5 c.c.) was used. The reaction mixture, after refluxing, was filtered hot, and the cooled filtrate, from which no solid separated, was then diluted with 5 vols. of water. The collected precipitate was extracted with boiling alcohol, leaving a residue, m. p. 230—240°, probably impure unchanged 2-hydroxy-5-cyanopyridine. The alcoholic extract deposited a semi-crystalline mass which was recrystallised from alcohol (50 c.c.) to give the required *compound*, m. p. 134—135° (2·9 g., 22%) (Found : C, 64·2; H, 4·5; N, 20·0. $C_{15}H_{12}O_2N_4$ requires C, 64·2; H, 4·3; N, 20·0%).

2-p-*Cyanostyrylpyridine.*—A mixture of *p*-cyanobenzaldehyde (2 g.), α-picoline (1·44 c.c.), and acetic

anhydride (1·45 c.c.) was refluxed for 10 hours. The mixture was cooled, treated with ice-water, and the solid collected, washed well with water, crystallised twice from alcohol, and dried in a vacuum at 78° to give the *cyanide*, m. p. 128—130° (1·3 g., 42%) (Found: N, 13·6. $C_{14}H_{10}N_2$ requires N, 13·6%).

2-*Styrylpyridine-4'-iminoether*.—A mixture of 2-*p*-cyanostyrylpyridine (0·8 g.), lime-dried alcohol (0·57 c.c.), and dry chloroform (10 c.c.) was saturated with dry hydrogen chloride below 0° and then left at 0° for 6 days. After treatment with sodium hydroxide in the usual manner, the chloroform solution of the iminoether was evaporated in a vacuum. The iminoether (m. p. 85—87°) which crystallised on cooling was washed with ligroin and dried in a vacuum (0·78 g., 80%). It was used for the preparation of the amidine without further purification.

2-p-*Amidinostyrylpyridine*.—A mixture of 2-styrylpyridine-4'-iminoether (0·75 g., 1 mol.), ammonium chloride (0·17 g., 1·05 mol.), and aqueous alcohol (1 c.c.; 4 c.c.) was heated at 60—65° for 7 hours and then left in a warm place (30—40°) for a further 16 hours. Concentrated hydrochloric acid was then added until the mixture was just acid to Congo-red, and the precipitated *dihydrochloride* of the amidine (0·57 g.) was filtered off, washed with acetone, and crystallised from alcohol containing a little water (30 c.c.; 1·5 c.c.). The amidine dihydrochloride separated at 0° in very pale yellow crystals, m. p. 282—283° (0·26 g., 42%) (Found: N, 13·9; Cl, 23·2; N : Cl = 3·04 : 2. $C_{14}H_{12}N_2,2HCl$ requires N, 14·2; Cl, 24·0%).

The authors wish to thank Drs. A. J. Ewins, F.R.S., and H. J. Barber for their interest in this work, Mr. S. Bance, B.Sc., A.R.I.C., and his staff for the semi-microanalyses, and the Directors of May and Baker Ltd. for permission to publish these results.

RESEARCH LABORATORIES, MAY AND BAKER LTD.,
DAGENHAM, ESSEX.

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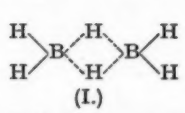
21. *Co-ordinate Links formed by Bonding Electrons: A Suggestion regarding the Structure of Diborane.*

By A. D. WALSH.

It is pointed out that there is no reason to suppose that the formation of the "co-ordinate link" type of bond is confined to lone-pair electrons. Bonding electrons, under certain conditions, may also be donated to an acceptor atom. The conditions for this to happen are discussed and shown to be sufficiently stringent for the phenomenon to be rare. The possibility that the structure of diborane may be formulated in terms of donation of bonding electrons to vacant boron atomic orbitals is discussed in detail. The suggestion is made that rearrangements of certain hydrocarbon cations may also be understood in terms of co-ordinate links formed by bonding electrons.

The Structure of Diborane and the Boron Hydrides.—Several recent papers (Longuet-Higgins and Bell, *J.*, 1943, 250; Bell and Longuet-Higgins, *Proc. Roy. Soc.*, 1945, *A*, **183**, 357; Pitzer, *J. Amer. Chem. Soc.*, 1945, **67**, 1126) have made it reasonably certain that diborane, B_2H_6, has a structure not like that of ethane but rather of a bridge type similar to that found in the aluminium halides such as Al_2Cl_6. Two hydrogen atoms occupy special positions somewhat as in (I). The interpretation of this structure in terms of electronic theory is less clear. Longuet-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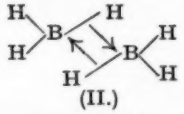
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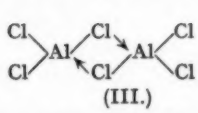
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Higgins and Bell (*loc. cit.*) attempted an interpretation in terms of resonance between structures containing only normal electron-pair bonds, but this was not completely satisfactory since it required additional postulates in order to explain why similar bridge structures were not found in certain other molecules. Burawoy (*Nature*, 1945, **155**, 328) supposed the central bonds to be similar to the "hydrogen bonds" found in, say, alcohols, but there are objections to this view, some of which have been expressed by Bell and Longuet-Higgins (*ibid.*, p. 328). There is little doubt that the structure is essentially dependent upon the existence of unfilled *L*-shell atomic orbitals of tervalent boron atoms. Pitzer (*loc. cit.*), realizing this, has described the bridge linkage as a "protonated double bond". A double bond is supposed to be formed from two BH_2^- units and in the anti-nodes of the second (π) bond two protons are embedded. The presence of the protons results in the B–B bond having a strength intermediate between those of double and single B–B bonds, though one would have thought that the magnitude of the B–B interaction found in the infra-red analysis (Bell and Longuet-Higgins, *loc. cit.*) was rather lower than this theory would indicate. Why protonated double bonds or their like are not more commonly found is not altogether clear.

Although not necessarily disagreeing with much of the descriptions of the diborane molecule

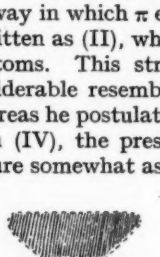
given by Longuet-Higgins and Bell and by Pitzer, the author thinks that another formulation is possible in language that is perhaps rather more familar and which may be helpful in explaining the rarity of occurrence of the bridge type of binding.

The idea of the "co-ordinate link" type of bond has long been familiar in valency theory.* If an atom, A, has an incomplete rare-gas structure and if another atom, B, has a lone pair of electrons, then B may "donate" its pair of electrons to form a bond between A and B. In terms of molecular orbitals, if B has a pair of electrons of wave function ψ_B and if A has an unfilled atomic orbital of wave function ψ_A, then on bringing A to B the initially ψ_B electrons of B will come to occupy a molecular orbital of form $a\psi_A + b\psi_B$; and if a and b are comparable in magnitude,† we say a co-ordinate link has been formed. It has always been assumed hitherto that the electrons "donated" to form a co-ordinate link must come initially from a lone pair. There is nothing in molecular orbital theory to indicate this, however. There is no sharp division between non-bonding and bonding filled orbitals: the paired electrons in each are qualitatively similar. The simple idea that we wish to suggest is the generalisation of the well-accepted concept of a co-ordinate link to include possible "donation" of bonding electrons as well as of lone-pair electrons.

In general, donation of bonding electrons will not be very noticeable because they are too strongly bound. It is usually true that lone-pair electrons are much less strongly bound than bonding electrons. It is not therefore surprising that, hitherto, "co-ordinate links" have only been found when formed from lone pair electrons. The conditions for a co-ordinate link to be formed include (1) the existence of an incomplete rare-gas electron shell in the acceptor atom and (2) a low ionisation potential for the donating electrons. These mean that the formation of co-ordinate links from bonding electrons will be rare.

B–H Bonds are known to be weak. For example, their stretching force constant in triborine triammine is only $3{\cdot}4 \times 10^5$ dynes/cm. as compared with $5{\cdot}0 \times 10^5$ dynes/cm. for the C–H bonds of methane and $6{\cdot}4 \times 10^5$ dynes/cm. for the N–H bonds of ammonia. Broadly speaking, there is a connection between force-constant values, bond strengths, and the ionisation potentials of bonding orbitals (Walsh, in course of publication). We think it safe to predict that the normal B–H bonding electrons have ionisation potentials at least as low as 10—12 v., *i.e.*, well within the range found for the ionisation energies of lone-pair electrons (cf. 10·8 v. for the lone-pair electrons of ammonia).

It is therefore possible to suppose that each B---H---B bond in the structure (I) consists of a filled molecular orbital of type $a\psi(\mathrm{BH}) + b\psi(\mathrm{B}:2p_z)$ binding the three nuclei B, B, and H (cf. the way in which π electrons in conjugated structures bind several nuclei); and that (I) may be rewritten as (II), where the arrows denote co-ordinate links from the B–H *bonds* to the adjacent B atoms. This structure closely resembles that usually written for Al_2Cl_6 (III). It has considerable resemblance to that proposed by Pitzer (*loc. cit.*), except in three respects. (1) Whereas he postulates the presence of filled σ and π orbitals between the boron atoms, somewhat as in (IV), the present suggestion is that two orbitals are occupied giving an electron-cloud picture somewhat as (V). (2) Pitzer's model predicts a "trigonal" arrangement of boron bonds



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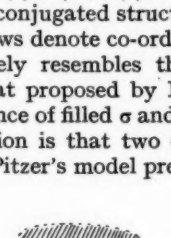

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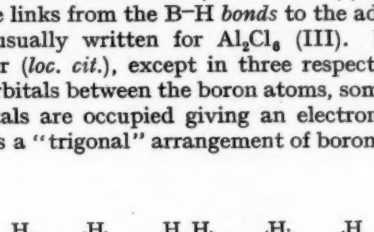


(VI.)

as in ethylene, *i.e.*, it supposes outer HBH angles close to 120°. According to the present description, the disposition of the bonds is essentially tetrahedral and the outer HBH angles should be close to 109°. The angle in the bridge structure for Al_2Me_6, as determined by electron

* It should be remembered, however, that, in certain cases, bonds previously represented by co-ordinate links are now known to be better represented by double bonds [*e.g.*, the higher oxides of elements in Groups V, VI, and VII (Phillips, Hunter, and Sutton, *J.* 1945, 146) and certain metallic carbonyls (Long and Walsh, *Trans. Faraday Soc.*, in the press)].

† An example where a and b are not equal in magnitude occurs in carbon monoxide (Long and Walsh, *loc. cit.*). In this case the bonding power of the occupied orbital that has in the past been described as a co-ordinate link is very small, so that the formula C=O is a better approximation than $\bar{\mathrm{C}}\equiv\overset{+}{\mathrm{O}}$, and the third occupied orbital in the bond might be better described as an "incipient co-ordinate link".

diffraction, is 110°. Pitzer's model implies a planar arrangement of all the nuclei except the two protons. A model according to the present suggestion shows that the planes of the two BH_2 units would be nearly but probably not quite identical. A slight lack of coplanarity of the two BH_2 units might possibly account for the imperfect fit of Pitzer's bridge model with the electron-diffraction data. Since in the wave function $a\psi(BH) + b\psi(B : 2p_z)$, the first term can itself be split into $c\psi(H) + b\psi(B : 2p_z)$, the two hydrogen atoms in the present (as in Pitzer's) model will be symmetrically placed with respect to the boron nuclei—as demanded by the infra-red spectrum. (3) The present model requires a close approach of the boron atoms without there being a strong boron–boron bond: of the two models, Pitzer's would seem to imply the stronger boron–boron bond.

It is probable that the polarity of the B–H bonds (B^+H^-) would assist the formation of structure (II), since (*a*) the partial positive charge on the boron atoms will enhance their acceptor properties, and (*b*) the polarity will mean that the point of maximum electronic density will lie well away from the boron atom initially concerned and so all the nearer to the other boron atom. The existence of such a third condition for a structure of type (II) to be stable would further explain the rarity of its occurrence. Trimethylborine may have insufficient B^+C^- polarity in its B–C bonds to form a stable dimer. Trimethylaluminium should have polarity in its Al–C bonds much as in the BH bonds of borine and it is not surprising that it may dimerise like borine. Boron trifluoride probably has too high an ionisation potential for its bonding electrons to form a type (II) structure. The explanation of why (VI) does not use the central B–H bond to form a further linkage may lie in the lack of sufficient positive charge on that boron atom.

As far as can be seen, the explanations possible on Pitzer's theory (Pitzer, *loc. cit.*; Longuet-Higgins, *J.*, 1946, 139) would also be possible on the present theory. Though a definite decision between the two theories must await further experimental evidence, we think the underlying idea of the present communication—that bonding electrons under certain conditions may form co-ordinate links—should be kept in mind. In particular, we think that the idea may prove helpful in understanding the electronic mechanism of certain molecular rearrangements of hydrocarbon cations and radicals.

The Mechanism of Certain Molecular Rearrangements.—We have in mind, particularly, those rearrangements, such as that of Wagner–Meerwein, which occur in cations of the type $CH_3\cdot\overset{+}{C}H_2$ (*i.e.*, containing an atom of even stronger acceptor properties than the boron atom of a BH_3 group). We have to suppose that sufficient deviation from the tetrahedral bond angles occurs for the electrons in the weakest bond on the saturated carbon atom (since these will be the least strongly bound bonding electrons) to become partly donated to the other carbon atom. Rearrangement in the *radical*, as well as in the ion (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 192—193), is not surprising because in both cases we should expect the actual electronic system (when a particular nuclear configuration is attained) to be described by a wave function of form $a\psi_A + b\psi_B$: with the radical this would be interpreted as a three-electron bond, with the ion as a co-ordinate link. The ratio $a : b$ will be determined by the bond energies in the initial and final states respectively of the rearrangement: if b is greater than a then, on approach of an appropriate anion, the full rearrangement will be likely to occur. In the change $CMe_3\cdot\overset{+}{C}H_2 \longrightarrow \overset{+}{C}Me_2\cdot CH_2Me$, since a secondary C–C bond is stronger than a tertiary, b will be greater than a and the rearrangement will occur. The change $CMe_3\cdot\overset{+}{C}HPh \longrightarrow \overset{+}{C}Me_2\cdot CHPhMe$, however, will not occur since a bond next but one to a phenyl group is weaker than usual (Walsh, *Trans. Faraday Soc.*, in the press) and a will be greater than b.

Though the language differs, this account includes much the same thought content as that in terms of " mesomerism " (see Watson, " Modern Theories of Organic Chemistry ", Oxford, 1941, p. 208). However, there are one or two advantages of the present formulation: (1) It shows that the bond on C_α which donates electrons to C_β (*i.e.*, the bond which may break on C_α and reform on C_β) will be, for example, a C–C rather than a C–H bond—since C–C bonds have ionisation energies less than 12 v., whereas C–H bonds have ionisation energies ~ 2 v. greater. In other words, a methyl group may migrate, but not a hydrogen atom. (2) It indicates a possible connection between a detail of the Wagner rearrangement and the structure of the boron hydrides.

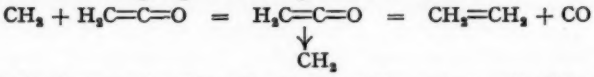
I am indebted to J. N. Agar for stimulating discussion and to C. A. Coulson, R. P. Bell, and H. C. Longuet-Higgins for kindly criticism.

LABORATORY OF PHYSICAL CHEMISTRY, CAMBRIDGE. [*Received, May 14th*, 1946.]

Note, added July 15th, 1946.—Since this paper was submitted for publication, Dewar (*J.*, 1946, 406) has published an account of benzidine-type rearrangements based on the idea that π electrons may be capable of forming dative bonds. However, there seems no reason to limit the idea to π electrons: it is not the symmetry properties of the orbital that determine the power of donation so much as its spatial spread, and this is determined primarily by the ionisation potential. Where a σ orbital has an ionisation potential less that that of a π orbital, it may act as a donor. We have discussed above the importance to the understanding of the structures of the boron hydrides of the expectation that B–H bonding electrons have a large spatial spread. The peroxide bond is also weak and its σ bonding orbital is therefore expected to have an extensive spatial distribution. This expectation is likely to prove of importance in the understanding of peroxide chemistry. For example, the well-known fact that ferrous ions can cause a splitting of the O–O bond may be due to the formation of an intermediate peroxide–ferrous ion complex, which can plausibly be formulated as

Other examples of the utility of the idea of co-ordinate links from bonding electrons may be selected as follows.

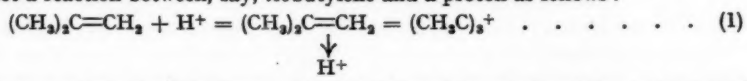
(1) The methylene molecule has proved unexpectedly difficult to observe. This may be explained as due to the facts that (*a*) its carbon atom has strong acceptor properties, and (*b*) it is usually produced in the presence of molecules such as keten or diazomethane containing bonds involving orbitals expected to have low ionisation potentials. The C=C bond of keten is known to be weaker, and therefore probably has a lower first ionisation potential, than that of ethylene (Walsh, in the press): it also has a lower ionisation potential than the C=O group and we expect the reaction



the second stage occurring because it reduces the energy of the system. Norrish, Crone, and Saltmarsh (*J.*, 1933, 1533) have indeed found this overall reaction to occur. In the complex, two electrons are binding three nuclei: these electrons occupy an orbital of form $a\psi_A + b\psi_B$, where ψ_A represents the π C–C orbital of keten and ψ_B the *L*-shell carbon atomic orbital that is vacant in the methylene molecule.

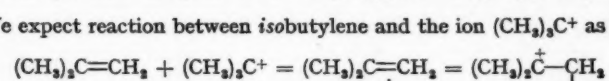
(2) Many reactions involving carbonium or hydrogen ions are likely to be capable of formulation in terms of these co-ordinate links, because of the strong acceptor properties of these ions. Good examples are to be found in Whitmore's scheme for the hydrogen ion-catalysed polymerisation of olefins (*Ind. Eng. Chem.*, 1934, **26**, 94):

Initiation.—We expect a reaction between, say, *iso*butylene and a proton as follows:



The overall reaction is that postulated by Whitmore. Minimisation of the energy of the systems results in the second step, $(CH_3)_3C^+$ and not $(CH_3)_2CH\cdot\overset{+}{C}H_2$ being formed because (*a*) the C=C polarity is such that the intermediate complex is already well towards $(CH_3)_3C^+$, and (*b*) a primary C–H bond is stronger than a secondary.

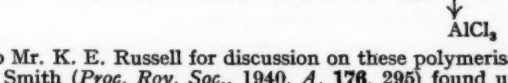
Propagation.—We expect reaction between *iso*butylene and the ion $(CH_3)_3C^+$ as follows:



the second step occurring for similar reasons to those given for (1), and the overall reaction being that postulated by Whitmore.

One sees the importance for ease of these reactions of a low ionisation potential for the olefin employed: *iso*butylene has a markedly lower π^{-1} ionisation potential (8·9 v.) than has ethylene itself (10·45 v.).

When Friedel–Crafts catalysts are employed in polymerisation or alkylation, the propagation step may be similar, but complications may occur of the form



(I am grateful to Mr. K. E. Russell for discussion on these polymerisation reactions.)

(3) Norrish and Smith (*Proc. Roy. Soc.*, 1940, *A*, **176**, 295) found unsaturated hydrocarbons to be very much more powerful quenchers than paraffins of the resonance radiation of sodium. They note that unsaturated molecules possess "large external fields" relative to the paraffins, and we may add to this that their results indicate that the effective quenching cross-section increases with decreasing π^{-1} ionisation potential for a series of olefins. The quenching action may therefore be conveniently described as due to the formation of a complex which may be formulated as

where the excited sodium atom is held by two electrons occupying an orbital $a\psi_A + b\psi_B$, where ψ_A is the original π orbital of the olefin and ψ_B is the original 3*s* orbital of the sodium atom. This complex only exists while the outer sodium electron is excited to leave vacant the 3*s* atomic orbital. As soon as it reverts to the ground state (*i.e.*, energy transfer occurs), dissociation of the complex must occur.

22. *The Rearrangement of* l-*Phenacyl-α-phenylethyldimethylammonium Bromide.*

By A. Campbell, A. H. J. Houston, and J. Kenyon.

The salt named in the title is smoothly converted by sodium hydroxide into the diastereoisomeric forms of ω-dimethylamino-ω-α-phenylethylacetophenone with almost complete retention of optical activity: the reaction therefore most probably involves an *intra*-molecular rearrangement.

One of the stereoisomerides can be quantitatively converted into the other in an almost optically pure condition, thus affording an example of an asymmetric transformation under the influence of a second optically active centre.

In a series of communications Stevens and his collaborators (*J.*, 1928—1932) have observed and investigated a transformation of quaternary ammonium salts which may be formulated as

$$R'\cdot CO\cdot CH_2\cdot \overset{+}{N}RMe_2\}\overset{-}{Br} + NaOH \longrightarrow R'\cdot CO\cdot CHR\cdot NMe_2 + H_2O + NaBr$$

The reaction, which was shown to be unimolecular, occurs only in an alkaline medium, and when a mixture of two salts in which R was different underwent reaction only the rearrangement products of each individual salt could be isolated: the rearrangement was accordingly considered to be intramolecular (Stevens, *J.*, 1930, 2107).

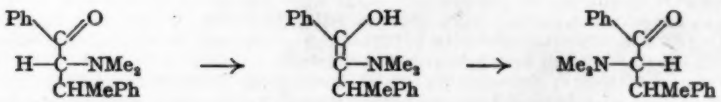
It seemed probable than an examination of the rearrangement products of an optically active quaternary ammonium salt, in which the migrating radical is attached to the rest of the molecule by an asymmetric carbon atom, would afford additional evidence bearing on the mechanism of this type of reaction, and the results of such a study are now presented.

Amongst the salts examined by Stevens was one in which R = CHMePh, prepared by the combination of ω-bromoacetophenone and *dl*-α-phenylethyldimethylamine: since this tertiary base is conveniently prepared from α-phenylethylamine which, in turn, is readily obtainable in an optically pure form, this quaternary ammonium salt was chosen for investigation. This salt reacted readily in sodium hydroxide solution, and since the resulting transformation product, (+)*ω-dimethylamino-ω-α-phenylethylacetophenone*, contains two asymmetric centres it was produced—as was found by Stevens in the case of the corresponding racemic compound—in two diastereoisomeric forms, both of which proved to be optically active.

One of these forms (α-) was converted into its l-*acid malate* which crystallised readily: on decomposition it yielded the α-base almost unchanged in rotatory power. When, however, a partly racemised specimen of the α-form was combined with *l*-malic acid and the salt crystallised, the liberated α-form possessed almost its maximum rotatory power. Furthermore, the second form (β-) on being heated with an alcoholic solution of sodium ethoxide was converted, apparently completely, into the corresponding α-form with $[\alpha]_{5893}^{20°}$ + 40·1° (in methanol). Under similar treatment the rotatory power of the optically pure α-form is reduced from $[\alpha]_{5893}^{20°}$ + 43·2° to + 39·7°—the rotatory powers of both specimens being raised to + 43·0° by crystallisation from methanol.

It therefore seems highly probable that both the α- and the β-form have been produced with almost complete retention of optical activity, and thus experimental evidence of a different character is provided in support of the view that the transformation of quaternary ammonium salts, described by Stevens, involves an intramolecular rearrangement.

Stevens suggested that the conversion of the racemic β-form into the racemic α-form might be effected by the groups arranged round the carbon atom next to the carbonyl group undergoing inversion by enolisation:



This explanation is rendered more probable by the retention of optical activity during the conversion of the β- into the α-variety. Furthermore, the conversion of the optically active β-form into the α-form in apparently quantitative yield affords an interesting example of an asymmetric transformation under the influence of another optically active centre. Had the enol ⟶ keto change followed its normal course, an equilibrium mixture of the α- and the β-form would have been obtained.

Experimental.

l-α-Phenylethylamine was obtained by applying a procedure briefly outlined by Betti (*Gazzetta*, 1920, **50**, 276) : to a solution of the *dl*-base (48 g., purified by one crystallisation of its acid oxalate) in 96% alcohol (600 c.c.) tartaric acid (59·6 g.) was added, and the mixture was kept at 60° and stirred for 24 hrs., then filtered whilst hot. The undissolved, compact, crystalline residue, recrystallised once from the minimum amount of hot water, yielded the optically pure acid tartrate of *l*-α-phenylethylamine, large rhombs (31 g.) with $[\alpha]_{5893}$ − 13·3°, $[\alpha]_{5780}$ − 13·5°, $[\alpha]_{5461}$ − 14·5°, $[\alpha]_{4358}$ − 16·2° (*l*, 2; *c*, 3·985) in aqueous solution at room temperature. The base was liberated by sodium hydroxide, and steam-distillation and extraction with benzene yielded *l*-α-phenylethylamine, b. p. 73°/14 mm. (14 g.). In the homogeneous state it had, at 17°, α_{5893} − 18·28°, α_{5780} − 19·24°, α_{5461} − 22·90°, α_{4358} − 37·44° (*l*, 0·5).

By fractional crystallisation of the corresponding *d*-bromocamphorsulphonate, Ingold and Wilson (*J.*, 1933, 1503) obtained the value $a^{16.5°}_{5461}$ − 22·92° (*l*, 0·5) for the base, so it is highly probable that optical purity has been reached by both procedures, of which the one described above is clearly more advantageous.

From the more soluble fractions of the acid tartrate salt there was obtained (*d* + *dl*)-α-phenylethylamine with $a^{20°}_{5461}$ + 12·32° (*l*, 0·5). An attempt was made to obtain the optically pure *d*-base by combining this material (24 g.) with racemic acid (29·8 g.) in alcoholic solution at 60° and stirring for 24 hrs. as described above. The crystalline residue on basification yielded, however, α-phenylethylamine (9 g.) with $a^{14°}_{5461}$ + 14·45° (*l*, 0·5). By the use of this highly active material for the preparation of *d*-α-phenylethylamine a considerable saving of *l*-malic acid would result (cf. *Org. Synth.*, II, 506).

l-α-*Phenylethyldimethylamine*.—*l*-α-Phenylethylamine hydrochloride (30 g.), m. p. 160°, $[\alpha]_{5893}$ − 3·7°, $[\alpha]_{5780}$ − 4·2°, $[\alpha]_{5461}$ − 4·5°, $[\alpha]_{4358}$ − 8·8°, (*l*, 2; *c*, 6·865 in aqueous solution), was dissolved in formalin (300 c.c.; 40%) and heated in a pressure bottle to 130° for 3 hrs. The resultant solution, after basification with sodium hydroxide, yielded l-α-*phenylethyldimethylamine* (9 g.), b. p. 81/16 mm., α_{5893} − 32·24°, α_{5780} − 33·92°, α_{5461} − 38·94°, α_{4358} − 70·6° (*l*, 0·5; *t*, 20°), $n_D^{14°}$ 1·5025, $d_4^{16°}$ 0·8986 (Found : N, 9·3. $C_{10}H_{15}N$ requires N, 9·4%). Its *picrate*, from alcohol, forms plates, m. p. 140—141°, $[\alpha]^{19°}_{5893}$ − 7·4° (*l*, 1; *c*, 1·621 in acetone) (Found : N, 14·6. $C_{16}H_{18}O_7N_4$ requires N, 14·9%).

l-*Phenacyl-α-phenylethyldimethylammonium Bromide*.—A solution of the above tertiary base (8 g.) and ω-bromoacetophenone (10·6 g.) in dry benzene (30 c.c.) after 2 days had deposited a pink crystalline mass; this, after recrystallisation from alcohol–ether (charcoal), yielded the *bromide*, large octagonal plates, m. p. 126°, $[\alpha]_{5893}$ − 71·0°, $[\alpha]_{5780}$ − 73·3°, $[\alpha]_{5461}$ − 85·9°, $[\alpha]_{4358}$ − 155° (*l*, 2 : *c*, 7·104 in ethanol); $[\alpha]_{5893}$ − 74·9°, $[\alpha]_{5780}$ − 78·4°, $[\alpha]_{5461}$ − 90·0°, $[\alpha]_{4358}$ − 156° (*l*, 2; *c*, 1·643 in acetone), both at room temperature (Found : Br, 23·0. $C_{18}H_{22}ONBr$ requires Br, 22·8%).

Conversion of l-*Phenacyl-α-phenylethyldimethylammonium Bromide into the Stereoisomeric* (+)-ω-*Dimethylamino-ω-α-phenylethylacetophenones*.—The *l*-quaternary bromide (11 g.) was warmed on the steam-bath with N-sodium hydroxide (50 c.c.) for 30 mins.; after a few minutes the solution deposited a yellow oil which solidified on cooling (*A*) (7·8 g.), m. p. 90—93°, $[\alpha]_{5893}$ + 25°, $[\alpha]_{5461}$ + 33° (*l*, 2; *c*, 1·66 in methanol).

Separation of the stereoisomerides. (*a*) By following the procedure adopted by Stevens (*J.*, 1930, 2113) this mixture (*A*) of diastereoisomerides was separated by fractional precipitation and fractional crystallisation of their picrates and there were obtained the *α-picrate*, yellow platelets, m. p. 194—196°, $[\alpha]^{19°}_{5893}$ + 7·98° (*l*, 1; *c*, 1·507 in acetone) (Found : N, 11·1. $C_{24}H_{24}O_8N_4$ requires N, 11·3%), and the *β*-picrate, stout prisms, m. p. 172—174°, $[\alpha]^{19°}_{5893}$ + 58·0° (*l*, 1; *c*, 2·586 in acetone) (for the corresponding racemic compounds, Stevens, *loc. cit.*, gives for the α-form, m. p. 186—187° and for the *β*-form, m. p. 174—176°).

On decomposition, the α-picrate yielded α-(+)-ω-*dimethylamino-ω-α-phenylethylacetophenone*, very pale yellow needles, m. p. 108°, from methanol (Found : N, 5·4. $C_{18}H_{21}ON$ requires N, 5·2%); $[\alpha]_{5893}$ + 84·2°, $[\alpha]_{5780}$ + 91·2°, α_{5461} + 114°, α_{4358} + 166° (*l*, 0·5; *c*, 1·993 in acetone; *t*, 21°); α_{5893} + 43·2°, α_{5780} + 46·3°, α_{5461} + 54°, α_{4358} + 83° (*l*, 0·5 : *c*, 1·814 in methanol; *t*, 21°).

The *β*-picrate, on decomposition, yielded the *β*-(+)-ω-*dimethylamino-ω-phenylethylacetophenone*, deep-yellow platelets, m. p. 108°, from acetone–light petroleum (Found : N, 5·4%); $[\alpha]_{5893}$ + 10·7° (*l*, 2; *c*, 2·017 in acetone), $[\alpha]_{5893}$ + 5·0° (*l*, 2; *c*, 2·258 in methanol). The intensity of the colour of the solutions made it impossible to measure the rotatory powers for other wave-lengths.

(*b*) A solution of the mixed optically active bases (*A*) (4 g.) in warm methanol deposited on cooling the almost pure α-base (1·9 g.); this, on crystallisation, yielded the pure α-base, m. p. 108°, $[\alpha]_{5893}$ + 43·5° in methanol. A second recrystallisation did not alter the rotatory power.

The original mother-liquors, on standing, deposited 0·7 g. of mixed α- and *β*-bases and, after concentration, the *β*-base (1·2 g.), which after crystallisation from acetone–light petroleum had m. p. 108°, $[\alpha]_{5893}$ + 5·3° in methanol.

This method of separation proved more effective with the resolved than with the unresolved bases owing to the greater difference in solubility between the α- and the *β*-form of the resolved diastereoisomerides, which are produced in the approximate ratio 4 : 3.

Determination of the Extent of Retention of Optical Purity of the Bases produced by the Rearrangement.—From a solution of the (+)-α-base (2·2 g.) and *l*-malic acid (0·8 g.) in 50% aqueous acetone the *hydrogen malate* of (+)-ω-dimethylamino-ω-α-phenylethylacetophenone separated in long needles, m. p. 118—119° (Found : N, 3·4. $C_{22}H_{27}O_6N$ requires N, 3·5%). The (+)-α-base regenerated from this salt had $[\alpha]^{20°}_{5893}$ + 43·8° (*l*, 0·5; *c*, 1·869 in methanol), compared with the original value $[\alpha]_{5893}$ + 43·2°.

The (+)-α-base (2 g.) was warmed on the steam-bath for 3 hrs. with a solution of sodium (2 g.) in alcohol (25 c.c.). Dilution with water precipitated the partly racemised α-base, m. p. 106—108°, $[\alpha]_{389}$ + 39·7° (in methanol); crystallisation of this from methanol raised its rotatory power to $[\alpha]_{5893}$ + 43·0° (in methanol).

Some slightly racemised (+)-*β*-base (2 g.), treated in the same manner, yielded almost optically pure

(+)-α-base, $[\alpha]_{5893}$ + 40·1°; this, after crystallisation from methanol, gave the optically pure (+)-α-base, $[\alpha]^{20°}_{5893}$ + 42·9° (in methanol).

Thanks are expressed to the Government Grants Committee of the Royal Society and to I.C.I. Ltd. for grants, to Messrs. May and Baker Ltd. for providing laboratory facilities for one of us (A. C.), and to Mr. S. Bance, B.Sc. for the microanalyses.

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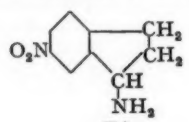
23. *The Synthesis of 5-Nitroindene.*

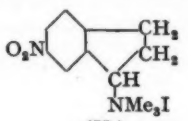
By ROBERT D. HAWORTH and DAVID WOODCOCK.

5-Nitroindene has been synthesised and its constitution established by reduction to 5-aminohydrindene.

DURING the course of other work it became necessary to prepare 5-nitroindene (III) and if possible the simple polymeric forms, analogous for example to di-indene (Stobbe and Farbe, *Ber.*, 1924, **57**, 1838).

Nitration of 1-hydrindamine yielded 6-nitro-1-hydrindamine (I) (Ingold and Piggott, *J.*, 1923, 1483), which gave excellent yields of the quaternary salt (II) on methylation with methyl iodide and sodium carbonate in methyl alcoholic solution. It was hoped to prepare 5-nitroindene (III) by the action of sodium or silver hydroxide on the salt (II) but unexpected results


(I.)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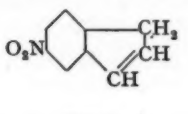
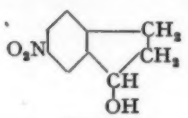

(III.)


(IV.)

were obtained. Although silver oxide readily converted the salt into the corresponding hydroxide, evaporation of the aqueous solution of the latter led to the elimination of trimethylamine and the precipitation of a black amorphous solid. The same substance was obtained even more conveniently by warming the iodide (II) with aqueous sodium hydroxide. Owing to the insolubility of the product, molecular weight determinations have not been possible, but the analytical results are consistent with a complex polymeric nitroindene structure. When 6-nitro-1-hydrindamine hydrochloride was warmed with sodium nitrite solution, it was converted into 6-*nitro*-1-*hydrindenol* (IV) from which a crystalline *acetate* and β-*naphthylurethane* were obtained. 6-Nitro-1-hydrindenol (IV) was converted into monomeric 5-*nitroindene* (III) by warming with 2N-hydrochloric acid. This nitro-compound (III) was volatile in steam and its constitution was established by reduction to 5-aminohydrindene and by conversion into 5-dimethylaminohydrindene methiodide.

This monomeric 5-nitroindene did not polymerise readily and simple polymers have not been obtained by the use of hydrochloric or syrupy phosphoric acids under conditions which result in the conversion of indene into di-indene. With concentrated sulphuric acid, however, it is converted into the black insoluble polymeric form previously mentioned.

EXPERIMENTAL.

6-*Nitro*-1-*hydrindenol* (IV).—A solution of 6-nitro-1-hydrindamine hydrochloride (2 g.) in water (20 c.c.) was treated with sodium nitrite (0·7 g. ≡ 1 mol.) in water (5 c.c.) and after heating the solution at 100° for ½ hour it was cooled, extracted with ether, the extract dried, and the solvent removed. Distillation of the residue at 0·8 mm. gave a yellow oil (1·05 g.) which solidified; the *compound* crystallised from aqueous methyl alcohol in stout prisms, m. p. 75—77° (Found: C, 59·6; H, 5·7. $C_9H_9O_3N$ requires C, 60·0; H, 5·6%). The *acetyl* derivative, prepared in the usual way, was obtained as prisms, m. p. 52—54°, from aqueous methyl alcohol (Found: C, 60·0; H, 5·3. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0%). The β-*naphthylurethane*, prepared by heating together equal weights of carbinol and β-naphthyl *iso*cyanate at 100° for two hours, was isolated as rosettes of slender rectangular prisms, m. p. 158—159°, by crystallisation from acetone–benzene (Found: C, 69·3; H, 5·0. $C_{20}H_{16}O_4N_2$ requires C, 69·0; H, 4·6%).

5-*Nitroindene* (III).—This was prepared by two methods. (*a*) 6-Nitro-1-hydrindenol (0·5 g.) and 2N-hydrochloric acid (5 c.c.) were refluxed for 20 minutes, cooled, extracted with chloroform, the extract dried, and the solvent removed. The residue crystallised from a small amount of methyl alcohol in rosettes of needles, m. p. 82—83° (0·23 g.) (Found: C, 66·8, 67·3; H, 4·9; C, 4·5. $C_9H_7O_2N$ requires 67·1; H, 4·4%). Dehydration by means of powdered potassium hydrogen sulphate at 140° gave

crystalline solids of varying m. ps.—possibly mixtures of the stereoisomers of 6-nitro-1-indanyl ether (see below).

(*b*) A solution of 6-nitro-1-hydrindamine hydrochloride (2 g.) in water (20 c.c.) was heated at 100° for ¾ hour with a solution of sodium nitrite (0·7 g.) in water (5 c.c.), then concentrated hydrochloric acid (25 c.c.) added and the whole refluxed for 1½ hours. Steam distillation, followed by extraction of the distillate with chloroform and removal of the solvent, left a residue (1·27 g.) which crystallised from methyl alcohol in needles, m. p. 81—82° undepressed by admixture with the *product* from method (*a*). The non-steam-volatile residue was a sandy coloured powder, which after a preliminary crystallisation from methyl alcohol–chloroform (charcoal) was separated by fractional crystallisation into rhombic prisms, m. p. 240° (Found : C, 63·7; H, 5·1. $C_{18}H_{16}O_5N_2$ requires C, 63·5; H, 4·7%), from chloroform, and slender rectangular prisms, m. p. 176—178° (Found : C, 63·6; H, 4·8%), from 50% methyl alcohol. A mixture of these two *substances*—probably diastereoisomeric forms of 6-nitroindanyl ether—melted at *ca.* 160°.

5-Aminohydrindene.—5-Nitroindene (0·2 g.) in methyl alcohol (10 c.c.) was shaken in hydrogen in the presence of palladised charcoal (15%) (0·1 g.) until no further uptake of gas was observed. Removal of the solvent from the filtered solution gave a brownish coloured oil, which was characterised by the formation of two derivatives :

(*a*) Treatment with excess acetic anhydride and sodium acetate at 100° for ½ hour gave a white solid after removal of excess of acetic anhydride and addition of water. Crystallisation from methyl alcohol gave 5-acetamidohydrindene as prisms, m. p. 102—104° (Lindner and Bruhin, *Ber.*, 1927, **60**, 435, give m. p. 106°).

(*b*) After being refluxed overnight in methyl alcoholic solution with excess of methyl iodide and sodium carbonate, the hot solution was filtered and concentrated to half its bulk; addition of ether gave 5-dimethylaminohydrindene methiodide, m. p. 192° (decomp.), raised to 195—196°(decomp.) by recrystallisation from methyl alcohol–ether (von Braun, Arkuszewski, and Köhler, *Ber.*, 1918, **51**, 292, give m. p. 190°) (Found : equiv., 313. Calc. for $C_{12}H_{18}NI$: equiv., 303).

5-Nitroindene Polymer—6-Nitro-1-indanyltrimethylammonium iodide (3 g.) was heated at 100° with a solution of potassium hydroxide (0·48 g. ≡ 1 mol.) in water (20 c.c.) until a black precipitate had formed. Steam distillation removed the trimethylamine formed and the black solid (1·1 g.) was collected at the pump, washed with dilute hydrochloric acid and water, and dried at 100°. It was insoluble in all the usual organic solvents [Found : C, 66·7; H, 4·6; N, 8·52, 8·54. $(C_9H_7O_2N)_x$ requires C, 67·1; H, 4·4; N, 8·7%]. Refluxing 5-nitroindene with either syrupy phosphoric or concentrated sulphuric acid gave an insoluble brownish amorphous material indistinguishable from the *product* described above.

Our thanks are due to the Director General of Scientific Research (Defence), Ministry of Supply, for permission to publish these results.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, May 14th*, 1946.]

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24. *A New Synthesis of Oxazoles and Iminazoles including its Application to the Preparation of Oxazole.*

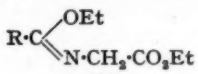
By J. W. CORNFORTH and (MRS.) R. H. CORNFORTH.

A synthesis of oxazoles and iminazoles is described. Some earlier work on oxazoles is discussed.

THE preparation of 2-methylbenzoxazole by Ladenburg (*Ber.*, 1876, **9**, 1525) marks the first recognition of oxazole as a ring system, but the name is due to Hantzsch (*ibid.*, 1887, **20**, 3118). The two most general oxazole syntheses are the condensation of α-halogeno-ketones with amides and the dehydration of α-acylamino-carbonyl compounds. It is possible that attempts have been made to prepare oxazole itself by both these methods, but we can find no report of this in the literature. In any case the methods are of limited application in the preparation of monosubstituted oxazoles, though satisfactory when a 2 : 5-diaryloxazole is required (cf. Robinson, *J.*, 1909, **95**, 2167; Lister and Robinson, *ibid.*, 1912, **101**, 1302).

The present work was facilitated by the observation of Schmidt (*Ber.*, 1914, **47**, 2548) that acetimidoethyl ether and glycine ethyl ester hydrochloride afford ethyl α-ethoxyethylideneaminoacetate (I; R = Me), the structure of which followed from its ready hydrolysis to glycine ethyl ester and ethyl acetate. We have confirmed this, and shown that substances of the type (I) are thermally more stable than Schmidt indicated. It has also been found that the reaction is a very general one. Thus the imidoethers from ethyl cyanoformate and ethyl or *iso*propyl alcohol gave respectively with glycine ester hydrochloride *ethyl ethoxycarbethoxymethyleneaminoacetate* (II; R = Et) and *ethyl* iso*propoxycarbethoxymethyleneaminoacetate* (II; R = Pr^{β}). Again, acetimidoethyl ether with the hydrochloride of ethyl aminomalonate gave *ethyl α-ethoxyethylideneaminomalonate* (III). Under different conditions the last reaction gave exclusively *ethyl 5-keto-2-methyl-4 : 5-dihydroiminazole-4-carboxylate-1-malonate* (IV), apparently by the reaction of (III) with ethyl aminomalonate (cf. Finger, *J. pr. Chem.*, 1907, **76**, 93). The

action of moist air on (III) also gave (IV), the first stage evidently being liberation of some ethyl aminomalonate by hydrolysis. Other substances of type (I) have been made and will be reported elsewhere.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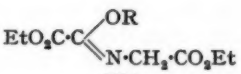
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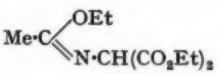
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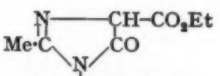
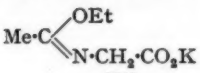

(IV.)

It was possible to saponify the ester (I; R = Me) under special conditions to *potassium α-ethoxyethylideneaminoacetate* (V). The free acid could not be isolated. The salt (V) with acetyl chloride gave a substance, $C_8H_{13}O_4N$, which gave ethyl acetate and acetylglycine on warming with water. This substance is considered to be *5-keto-2-ethoxy-3-acetyl-2-methyltetrahydro-oxazole* (VI) rather than the mixed anhydride (VII), for reasons given in the experimental section.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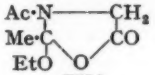
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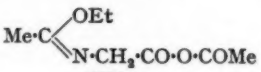
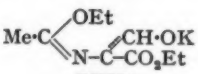
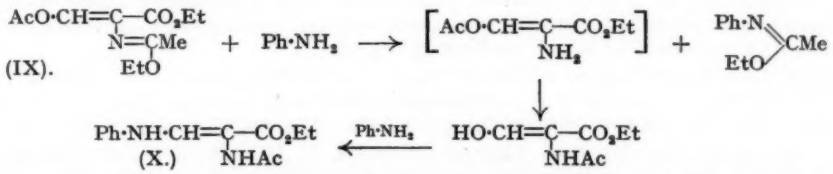

(VII.)

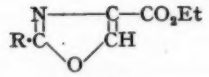

(VIII.)

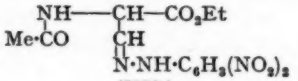
Formylation of (I; R = Me) by ethyl formate and potassium ethoxide gave *potassium ethyl α-(α-ethoxyethylideneamino)-β-hydroxyacrylate* (VIII); this product still gave ethyl acetate on hydrolysis with aqueous acid and must therefore carry the hydroxymethylene group in the position shown. Acetic anhydride on the salt gave the *acetoxymethylene* compound (IX), reconverted into the salt (VIII) by cold alcoholic potash. The action of aniline on (IX) gave *ethyl β-anilino-α-acetamidoacrylate* (X), the reaction evidently proceeding by capture of the ethoxyethylidene group by aniline, followed by intramolecular acylation and reaction with another molecule of aniline :

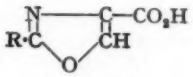

(IX.)

(X.)

The action of hydrogen chloride in ether on the salt (VIII) gave by loss of the elements of potassium ethoxide a product which can only be formulated as *ethyl 2-methyloxazole-4-carboxylate* (XI; R = Me); the properties of the substance are in accord with this view. The yield was low until it was discovered that decomposition of the potassium salt at higher temperatures was advantageous, and that good yields could be obtained by distilling a mixture of the salt with benzoic acid, or best by gradually adding the salt to boiling acetic acid.


(XI.)


(XII.)


(XIII.)

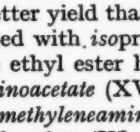
Reaction of the ester (XI; R = Me) with 2 : 4-dinitrophenylhydrazine in hydrochloric acid gave *ethyl acetamidoformylacetate dinitrophenylhydrazone* * (XII). The other oxazoles mentioned in this paper also reacted with 2 : 4-dinitrophenylhydrazine. A ring-scission of this type is apparently new in the oxazole series, but Gabriel (*Ber.*, **1910**, **43**, 136) hydrolysed 2 : 5-diphenyloxazole to benzoic acid and aminoacetophenone with hydrochloric acid under pressure.

The ester (XI; R = Me) with aqueous alkali gave *2-methyloxazole-4-carboxylic acid* (XIII; R = Me). Oesterreich (*Ber.*, 1897, **30**, 2254) obtained from the oxidation of 2 : 4-dimethyloxazole an acid to which he gave this formula, on the basis of a single nitrogen estimation. It is certainly not identical with our acid and is perhaps 4-methyloxazole-2-carboxylic acid : Oesterreich's choice of the 4-methyl group as the seat of oxidation seems to be founded on a faulty analogy.

The acid (XIII; R = Me) readily lost carbon dioxide on heating in quinoline with a little copper oxide to give *2-methyloxazole* (XIV; R = Me). This was characterised as the *picrate*.

* The structure of this substance and of the anil (X) has been confirmed by a synthesis starting from ethyl formylchloroacetate. The work will be published later.

It now became of interest to attempt the synthesis of oxazole by the new method. The first difficulty was that formimido-ethers are not stable enough to be condensed with glycine ester hydrochloride in the usual way. The variation was tried of adding a mixture of the hydrochlorides of formimidoethyl ether and glycine ethyl ester to one molecular proportion of aqueous alkali under ether. There were indications that the right product was formed, but was too unstable to be isolated. Fortunately our experience with the derivatives (II) from ethyl cyanoformate had shown that the *iso*propoxy-compound (II; R = Pr^{β}) was more stable and formed in better yield than its ethoxy-analogue.* Following this indication, hydrogen cyanide was condensed with *iso*propanol to give *formimido*iso*propyl ether hydrochloride*, which, treated with glycine ethyl ester hydrochloride in the manner indicated above, gave *ethyl* iso*propoxymethyleneaminoacetate* (XV). This was formylated as before, and the resulting *potassium ethyl* α-iso*propoxymethyleneamino*-β-*hydroxyacrylate* (XVI) added to boiling acetic acid, when *ethyl oxazole*-4-*carboxylate* (XI; R = H) was formed. Alkaline hydrolysis gave *oxazole*-4-*carboxylic acid* (XIII; R = H), which in quinoline was decarboxylated smoothly to *oxazole* (XIV; R = H). The yields in this synthesis were good, with the exception of the cyclisation (34%).



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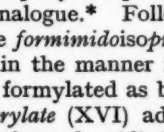
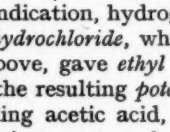


(XV.)



(XVI.)

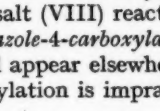
The low basicity and high volatility of oxazole tend to make its salts unstable. Thus the picrate and hydrochloride were both obtained crystalline; but the picrate became picric acid within a few minutes of being collected, and the hydrochloride vanished in a vacuum desiccator. A mercuric chloride complex (described later) is the most satisfactory derivative found so far, but cannot be kept. It may be noted that oxazole-4-carboxylic esters appear to be too weakly basic to form salts under ordinary conditions.

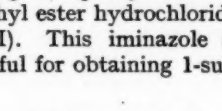
It is proposed to explore the applicability of this method as a general synthesis of oxazoles. The condensation of imidoethers with α-amino-aldehydes and -ketones or with α-amino-β-keto-esters is an obvious extension on which we hope to report.

Conversion of an oxazole into an iminazole was first achieved by Lewy (*Ber.*, 1888, **21**, 2194), who found it necessary to heat 4-phenyl-2-methyloxazole with alcoholic ammonia for sixteen hours at 220—230° in order to obtain the iminazole. We found that 2-methyloxazole-4-carboxylic acid reacted rapidly with aqueous ammonia at 150° to give 2-methyliminazole. Further, on boiling the acid with aniline 1-*phenyl*-2-*methyliminazole* (XVII; R = Me) was formed. We have not yet determined whether 2-methyloxazole will form iminazoles with equal facility. Oxazole-4-carboxylic acid with aniline gave 1-*phenyliminazole* (XVII; R = H).

The potassium salt (VIII) reacted with glycine ethyl ester hydrochloride in the cold to give *ethyl* 2-*methyliminazole*-4-*carboxylate*-1-*acetate* (XVIII). This iminazole synthesis, of which other examples will appear elsewhere, may prove useful for obtaining 1-substituted iminazoles where direct *N*-alkylation is impracticable.

(XVII.)





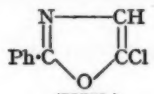
(XVIII.)

Two further matters relating to oxazole chemistry will now be discussed. In the first place, Schwanert (*Annalen*, **1859**, **112**, 59) distilled hippuric acid with phosphorus pentachloride and obtained two products, C_9H_6ONCl and $C_9H_5ONCl_2$. The former (m. p. between 40° and 50°, b. p. about 220°) has the properties which would be expected of 5-chloro-2-phenyloxazole (XIX); the latter is probably the 4 : 5-dichloro-derivative. Rügheimer (*Ber.*, 1886, **19**, 1169) formulated these products as 1-chloro- and 1 : 3-dichloro-4-hydroxy*iso*quinoline, though to explain their insolubility in alkali he wrote them in the keto-form.†

* For making substances of type (I) from unreactive cyanides, on the other hand, it is best to make the imidoether with methanol; the speed and completeness of imidoether formation outweighs a somewhat lower yield in the condensation with glycine ester hydrochloride.

† Rügheimer carried out an indecisive experiment on the reduction of the product $C_9H_5ONCl_2$ (or of a substance $C_9H_5NCl_6$ obtained by heating it with phosphorus pentachloride at 170°; the paper is ambiguous on this point) with hydriodic acid at 200°. It is surprising to find this work referred to by Hollins (" Synthesis of Nitrogen Ring Compounds ", 1924) in the following terms: " Hippuric acid itself is converted by PCl_5 into a dichloroanhydro compound from which *iso*quinoline is obtained by reduction with HI ". Actually there is no definite evidence in the paper cited that *iso*quinoline was formed at all.

This interpretation cannot be upheld : the boiling points are much too low for *iso*quinoline derivatives; also 1-chloro-4-hydroxy*iso*quinoline has been made (Gabriel and Colman, *Ber.*, 1900, **33**, 986), and shows no resemblance to the product C_9H_6ONCl.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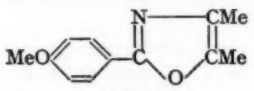
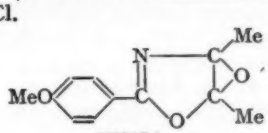
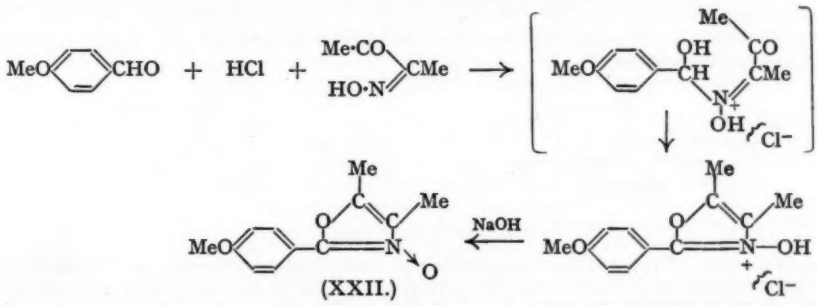

(XX.)

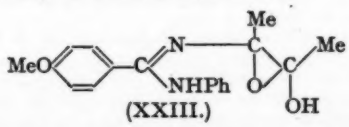

(XXI.)

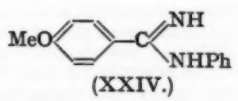
The second point refers to one of the oxazole syntheses more recently discovered, namely that of Diels and Riley (*Ber.*, 1915, **48**, 897), which was confirmed and extended by Dilthey and Friedrichsen (*J. pr. Chem.*, 1930, **127**, 292). The condensation of diacetyl monoxime with anisaldehyde in hydrochloric acid gave a basic substance, $C_{12}H_{13}O_3N$, which easily lost an oxygen atom to zinc dust and water, giving 2-(*p*-methoxyphenyl)-4 : 5-dimethyloxazole (XX). The intermediate was formulated as 2-(*p*-methoxyphenyl)-4 : 5-dimethyl-4 : 5-epoxy-4 : 5-dihydro-oxazole (XXI), a conclusion with which we do not agree.

The base $C_{12}H_{13}O_3N$ crystallised as a hydrate from water : when anhydrous it was sensitive to light. It was stable to acid and alkali, and liberated iodine on warming with potassium iodide solution. All these properties suggest an *N*-oxide (XXII), and the reaction becomes simply the *N*-alkylation of an oxime, with subsequent ring-closure :


(XXII.)

No mechanism for the formation of (XXI) has been suggested, and indeed it is difficult to do so, or to explain why an ethylene oxide is produced under conditions so favourable for its destruction. Dilthey and Friedrichsen (*loc. cit.*) mention the formula (XXII) among others as a possibility, but give preference to the formula (XXI). The experimental evidence on which formula (XXI) is based needs to be reviewed. The easy reduction to an oxazole fixes the position of all atoms except the labile oxygen. Diels and Riley found that the substance on treatment with aniline at 100° gave by addition a product $C_{18}H_{20}O_3N_2$. This with aqueous oxalic acid broke down to diacetyl and an oxalate, m. p. 157°, which yielded anisamide and aniline on treatment with cold sodium bicarbonate solution. On this evidence the remarkable structure (XXIII) was given to the product $C_{18}H_{20}O_3N_2$ and the oxalate was considered to be that of *N*-phenylanisamidine (XXIV).

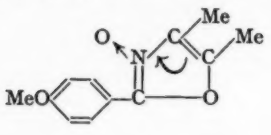

(XXIII.)

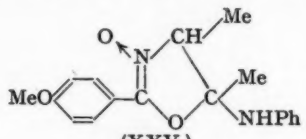

(XXIV.)

Analysis of the oxalate [Found : C, 55·2, 55·1; H, 5·1, 5·2; N, 7·0, 7·4; $(CO_2H)_2$, 25·4%] made it necessary to assume the presence of two molecules of water, neither of which was expelled by drying at 139° in a vacuum. Even so, the agreement is not good [$C_{14}H_{14}ON_2,(CO_2H)_2,2H_2O$ requires C, 54·5; H, 5·7; N, 7·9; $(CO_2H)_2$, 25·6%]. Examination of the literature shows that substances of the type (XXIV), *e.g.*, *N*-phenylbenzamidine, are certainly not so unstable as to be decomposed on liberation from their salts by weak bases. In the example cited it is necessary to heat the base with water to 120°, and the products are aniline, ammonia, benzoic acid, and benzanilide (anything but benzamide !). We suggest that the oxalate, m. p. 157°, obtained by Diels and Riley is a mixture of anisamide oxalate with a little aniline hydrogen oxalate. Anisamide with oxalic acid in methanol readily gives *anisamide oxalate*, and we found that by crystallising a mixture of oxalic acid (2 mols.), aniline (1 mol.),

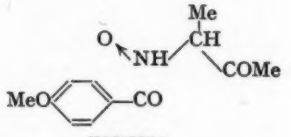
and anisamide (2 mols.) twice from methanol, a crystalline product was obtained, m. p. 152—154°: thus not far from that reported by Diels and Riley. The calculated figures for anisamide oxalate containing 8% of aniline hydrogen oxalate are C, 54·9; H, 5·1; N, 7·15; $(CO_2H)_2$, 25·1%, in excellent agreement with the values quoted, and with the observed behaviour of the product.

On the basis of formula (XXII) for the substance $C_{12}H_{13}O_3N$, it is easily seen that the N→O group would facilitate addition to the C=C double bond:





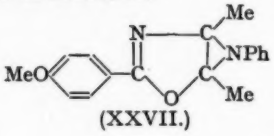
(XXV.)



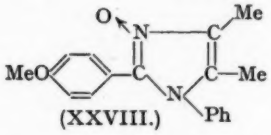
(XXVI.)

and that the aniline adduct would then be (XXV). The first stage of hydrolysis would give aniline and the intermediate (XXVI), which passes to diacetyl and anisamide by a type of intramolecular oxidation well known among *N*-oxides.

Diels and Riley also studied the action of phenyl *iso*cyanate on the substance $C_{12}H_{13}O_3N$, obtaining in poor yield a product, $C_{18}H_{18}O_2N_2$, which was formulated as (XXVII). In our view the product would probably be (XXVIII). Diels and Riley believed that the labile oxygen atom was involved in this reaction, chiefly because the product was not reduced by zinc dust and water. This is hardly a valid objection to formula (XXVIII): *N*-oxides vary greatly in ease of reduction.



(XXVII.)



(XXVIII.)

Experimental.

Anisamide Oxalate.—Prepared from anisamide and oxalic acid in methanol, this *salt* formed colourless leaflets, m. p. 184° (decomp.) [Found: C, 55·3; H, 5·0. $2C_8H_9O_2N,(CO_2H)_2$ requires C, 55·1; H, 5·1%].

Ethyl α-Ethoxyethylideneaminoacetate (I; R = Me).—This was obtained essentially as described by Schmidt (*loc. cit.*) from acetimidoethyl ether and glycine ethyl ester hydrochloride. It was found advisable, however, to wash the ethereal solution with water before drying it. This seems to remove some substance (amidine?) which catalyses decomposition on distillation. Thus we found, contrary to Schmidt, that the product can be distilled on the water-pump without injury; b. p. 85—86°/7·5 mm., 100—101°/19 mm. The best yield was 68% of distilled product.

Ethyl Ethoxycarbethoxymethyleneaminoacetate (II; R = Et).—Ethyl cyanoformate (9·9 g.) with ethyl alcohol (4·6 g.) in ether (15 c.c.) was treated below 0° with dry hydrogen chloride (3·7 g.). Crystallisation soon set in. The salt was washed with ether and decomposed below 0° with a strong solution of potassium carbonate (14 g.) and ether. The ethereal solution was shaken for 1 hour with glycine ethyl ester hydrochloride (14 g.) and water (8 c.c.). The ether layer was washed with water, dried (Na_2SO_4), and evaporated. The residue on distillation gave the *ester* as a colourless oil (1·6 g.), b. p. 78—80°/0·06 mm., which quickly reddened in air (Found: C, 51·8; H, 7·3. $C_{10}H_{17}O_5N$ requires C, 51·9; H, 7·4%).

Ethyl iso*Propoxycarbethoxymethyleneaminoacetate* (II; R = Pr^{β}).—Prepared as above, using *iso*propyl alcohol (6·0 g.) instead of ethyl alcohol, this *ester* (5·9 g.) was a colourless oil, b. p. 76—78°/0·04 mm. (Found: C, 54·1; H, 7·7. $C_{11}H_{19}O_5N$ requires C, 53·9; H, 7·8%).

Ethyl α-Ethoxyethylideaminomalonate (III).—Acetimidoethyl ether hydrochloride (9·6 g.; 50% excess) was converted into the base in the usual way with ether and potassium carbonate. The ether solution (*ca.* 100 c.c.) was shaken with ethyl aminomalonate hydrochloride (10·5 g.) and water (5 c.c.) for 2 hours. The ether layer was washed twice with very dilute hydrochloric acid (to remove ethyl aminomalonate), dried, and evaporated. The *ester* distilled at 82°/0·05 mm. as a colourless odourless mobile oil (7·5 g.; 60%) (Found: C, 53·7; H, 7·8; N, 5·8. $C_{11}H_{19}O_5N$ requires C, 53·9; H, 7·8; N, 5·7%).

Ethyl 5-Keto-2-methyl-4 : 5-dihydroiminazole-4-carboxylate-1-malonate (IV).—In an earlier experiment when no excess of acetimidoethyl ether was taken, and the washing with acid omitted, the product on attempted distillation reacted rapidly to give a crystalline solid. The *iminazolone* crystallised from alcohol or chloroform–light petroleum in colourless prisms, m. p. 208—209° (decomp.) after reddening at 200° (Found: C, 51·0; H, 6·3; N, 8·5. $C_{14}H_{20}O_7N_2$ requires C, 51·2; H, 6·1; N, 8·5%).

Potassium α-Ethoxyethylideneaminoacetate (V).—Potassium (0·36 g.) was dissolved in alcohol (1·1 g.) and ether (8 c.c.). The solution was diluted with ether (100 c.c.), and the ester (I, R = Me) (1·7 g.) added, followed by water (0·2 c.c.). Crystallisation was complete within a few minutes. The *salt* was collected and washed with ether (Found: N, 7·0. $C_6H_{10}O_3NK$ requires N, 7·6%). It was a white hygroscopic powder and with dilute acid was hydrolysed very rapidly to ethyl acetate and glycine.

5-Keto-2-ethoxy-3-acetyl-2-methyltetrahydro-oxazole (VI).—The salt (V) (6 g.) was shaken in ether with acetyl chloride (2·6 g.); after a few minutes the solution was filtered and distilled. The *oxazolidone*

(2·25 g.) came over at 96—98°/0·15 mm. as a colourless viscid oil, which eventually solidified to a crystalline mass, m. p. 45—46° (Found : C, 51·3; H, 7·0. $C_8H_{13}O_4N$ requires C, 51·4; H, 7·0%). The substance was readily soluble in water. On warming with water, N-hydrochloric acid, or phosphate buffer (pH 8), it gave ethyl acetate and acetylglycine, and no free glycine could be detected by the ninhydrin test. Boiling with alcohol also led to acetylglycine. This behaviour determined the choice of formula (VI), as it was concluded that the acetyl group must already be attached to nitrogen.

Potassium Ethyl α-(α-Ethoxyethylideneamino)-β-hydroxyacrylate (VIII).—Potassium * (4·5 g.) in ether (50 c.c.) was treated with alcohol (16·7 c.c.). The resulting solution was diluted with ether to 200 c.c., cooled below 0°, and treated with a mixture of the ester (I; R = Me) (20 g.) and ethyl formate (13 g.). After 1 hour, ether (300 c.c.) was added. The crystalline potassium *salt* was collected after being kept overnight at 0°, washed with ether, and freed from solvent under reduced pressure. It formed a light yellow hygroscopic powder (24 g.; 87%) (Found : N, 5·8. $C_9H_{14}O_4NK$ requires N, 5·9%). On careful addition of alcoholic ferric chloride to a dilute alcoholic solution of the salt, a deep violet colour appeared, which faded quite suddenly to a light brown as more reagent was added.

Ethyl α-(α-Ethoxyethylideneamino)-β-acetoxyacrylate (IX).—The salt (VIII) (11 g.) was stirred into acetic anhydride (15 c.c.). After ½ hour ether and sodium bicarbonate solution were added with ice cooling. The ether solution was dried and evaporated, and the residue fractionated. The *acetoxy-ester* (8·1 g.; 72%) distilled as a colourless oil, b. p. 155—159°/15 mm., 88—90°/0·1 mm. (Found : C, 54·7; H, 7·3; N, 5·8. $C_{11}H_{17}O_5N$ requires C, 54·3; H, 7·0; N, 5·8%). With cold alcoholic potash the potassium salt (VIII) was regenerated, as shown by the characteristic behaviour with alcoholic ferric chloride. On boiling with water, ethyl acetate and acetic acid were liberated; the other products appeared to contain the oxazole ester (XI; R = Me). With aqueous ferric chloride a red-purple colour slowly developed.

Ethyl β-Anilino-α-acetamidoacrylate (X).—The acetoxy-ester (IX) (2 g.) was mixed with aniline (1·5 g.): the mixture became warm. After ½ hour reaction was completed by warming for a minute on the steam-bath. N-Hydrochloric acid (10 c.c.) was now added. The product soon crystallised and was recrystallised once from 50% alcohol and once from chloroform–light petroleum. The *anil* formed colourless, silky needles, m. p. 167—168° (Found : C, 63·1; H, 6·3; N, 11·4. $C_{13}H_{16}O_3N_2$ requires C, 62·9; H, 6·4; N, 11·3%). With 2 : 4-dinitrophenylhydrazine (1% in 2N-hydrochloric acid) it slowly gave the dinitrophenylhydrazone (XII).

Ethyl 2-Methyloxazole-4-carboxylate (XI; R = Me).—The salt (VIII) (25 g.) was added during 10 minutes to boiling acetic acid (50 c.c.). The solution was distilled at low pressure, and after acetic acid the *ester* (12·2 g.; 75%) distilled as a colourless oil, b. p. 106—110°/12 mm., which solidified in massive prisms, m. p. 24—25° (Found : C, 54·5; H, 6·0. $C_7H_9O_3N$ requires C, 54·2; H, 5·8%).

Ethyl Acetamidoformylacetate 2 : 4-Dinitrophenylhydrazone (XII).—The ester (XI; R = Me) was kept with a slight excess of 2 : 4-dinitrophenylhydrazine (0·5% in 2N-hydrochloric acid). After 2 days the yellow needles were collected and crystallised from alcohol, giving the *hydrazone*, m. p. 183—184° (Found : N, 19·5. $C_{12}H_{13}O_7N_5$ requires N, 19·8%).

2-Methyloxazole-4-carboxylic Acid (XIII; R = Me).—The ester (XI; R = Me) was hydrolysed by heating with a slight excess of aqueous potassium hydroxide for ½ hour on the steam-bath. Alcohol was removed at low pressure, and the solution was acidified (Congo-red) and extracted continuously with ether. The ether on evaporation left the acid as a hydrate, from which water was removed by drying over sulphuric acid in a vacuum. The *acid*, obtained in almost quantitative yield, crystallised from alcohol–benzene in colourless plates, m. p. 183—184° with slow decomposition (Found : C, 47·3; H, 4·2; N, 10·9. $C_5H_5O_3N$ requires C, 47·2; H, 3·9; N, 11·1%).

2-Methyloxazole (XIV; R = Me).—The acid (XIII; R = Me) (5 g.) was heated with quinoline (25 g.) and a little copper oxide in a bath at 180—200°. The distillate was collected over solid potassium hydroxide. The quinoline was finally boiled for a short time. The distillate was redistilled over fresh alkali, giving *2-methyloxazole* (2·6 g.; 80%) as a colourless liquid of pyridine-like odour, b. p. 87—88°, $n_D^{16.5°}$ 1·4347 (Found : C, 58·0; H, 6·4. C_4H_5ON requires C, 57·8; H, 6·0%). The *picrate* crystallised from alcohol in fine yellow needles, m. p. 116—117° (Found : C, 38·3; H, 2·6; N, 17·9. $C_4H_5ON,C_6H_3O_7N_3$ requires C, 38·5; H, 2·6; N, 18·0%).

Formimidoisopropyl Ether Hydrochloride.—Hydrogen chloride (54 g.) was passed into a mixture, cooled below 0°, of hydrogen cyanide (39·9 g.), *iso*propyl alcohol (89 g.), and ether (350 c.c.). After four days at 0° the crystalline *salt* (158·5 g.; 87%) was collected and washed with ether. It formed colourless leaflets, m. p. 117—118° (decomp.). Analysis indicated the presence of a little ammonium chloride, as is usual in formimidoether hydrochlorides (Found : N, 12·2. $C_4H_{10}ONCl$ requires N, 11·3%).

Ethyl iso*Propoxymethyleneaminoacetate* (XV).—The above salt (15·2 g.) with glycine ethyl ester hydrochloride (17·2 g.) was added at 0° to potassium hydroxide (27 c.c. of 25%) under ether (200 c.c.). After 5—10 minutes' shaking the ether was decanted, the salt sludge washed twice with fresh ether, and the united ether extracts washed with a little water, dried (Na_2SO_4), and evaporated. Distillation gave the *ester*, b. p. 99°/19 mm. (12·2 g.; 57%), as a colourless oil (Found : C, 55·1; H, 8·7; N, 8·3. $C_8H_{15}O_3N$ requires C, 55·5; H, 8·7; N, 8·1%).

*Potassium Ethyl α-*iso*Propoxymethyleneamino-β-hydroxyacrylate* (XVI).—A solution was prepared from potassium (20·2 g.), alcohol (60 g.), and ether (250 c.c.); it was diluted to 1500 c.c. with ether, cooled to 0°, and treated with a mixture of the ester (XV) (86 g.) and ethyl formate (55 g.). Precipitation began at once. Next day the potassium *salt* (91 g.; 82%) was collected and washed with ether. It formed a light yellow hygroscopic crystalline powder (Found : N, 6·1. $C_9H_{14}O_4NK$ requires N, 5·9%) which turned sticky on being kept, even in a desiccator. It showed with alcoholic ferric chloride the same characteristic colour changes as the potassium salt (VIII).

* This metal is quickly and efficiently freed from crust by boiling with dioxan. The same method can be used to recover potassium from scrap : the globules of molten metal rise to the surface and are made to coalesce by cautious addition of a few drops of alcohol.

Ethyl Oxazole-4-carboxylate (XI; R = H).—The potassium salt (XVI) (5 g.), was added during 10 minutes to boiling acetic acid (10 c.c.). Direct distillation gave 1·0 g. (34%), b. p. 106—110°/20 mm. The product from a number of runs was redistilled, giving the *ester*, b. p. 101—102°/14 mm., as a colourless oil, which during one distillation suddenly solidified. Crystallisation from benzene–light petroleum gave colourless prisms, m. p. 47—49° (Found: C, 51·4; H, 4·6; N, 10·2. $C_6H_7O_3N$ requires C, 51·1; H, 4·9; N, 9·9%).

Oxazole-4-carboxylic Acid (XIII; R = H).—The ester (XI; R = H) (14·2 g.) was hydrolysed as described for its homologue. The acid separated during ether extraction in massive hydrated crystals. The product of ether extraction was ground and kept for 24 hours over sulphuric acid in a vacuum, leaving anhydrous *oxazolecarboxylic acid* (10·4 g.; 91%). A portion crystallised from alcohol–benzene had m. p. 142° (Found: C, 42·5; H, 3·0; N, 12·4. $C_4H_3O_3N$ requires C, 42·5; H, 2·7; N, 12·4%). The hydrated form melted at about 100° before solidifying and melting at 142°.

Oxazole (XIV; R = H).—The above acid (5 g.) was decarboxylated in the manner previously described, giving *oxazole* (2·3 g.; 75%) as a colourless mobile liquid of strong pyridine-like odour, b. p 69—70°, $n_D^{17.5°}$ 1·4285 (Found: C, 52·0; H, 4·5; N, 20·5. C_3H_3ON requires C, 52·2; H, 4·4; N, 20·3%). The picrate and hydrochloride have been mentioned above. On addition of oxazole to aqueous mercuric chloride a crystalline complex separated, m. p. 148° when rapidly heated. Slow heating gave no m. p. below that of mercuric chloride. Oxazole was also lost over sulphuric acid.

The absorption spectrum of oxazole has been examined by Dr. F. B. Strauss. Absorption begins below 2400 A. and has the value $\varepsilon_{molar} = 30$ at 2300 A. There is probably a maximum below 2000 A.

2-*Methyliminazole*.—2-Methyloxazole-4-carboxylic acid (1 g.) was heated for 1 hour at 150° in a sealed tube with aqueous ammonia (10 c.c.; *d* 0·88). The solution was evaporated at low pressure and the residue crystallised three times from benzene, giving 2-methyliminazole (140 mg.), long colourless needles, m. p. 141—143°* (Found: C, 58·0; H, 7·3. Calc. for $C_4H_6N_2$: C, 58·5; H, 7·3%). The picrate crystallised from water in yellow needles, m. p. 215° (corr.) [Fargher and Pyman, *J.*, 1919, **115**, 231, give m. p. 213° (corr.)].

1-*Phenyl*-2-*methyliminazole* (XVII; R = Me).—2-Methyloxazole-4-carboxylic acid (1 g.) was boiled with aniline (2 c.c.) for ½ hour. After two fractionations the colourless oily *base* (0·83 g.) had b. p. 147°/20 mm. (Found: C, 76·0; H, 6·3. $C_{10}H_{10}N_2$ requires C, 76·0; H, 6·3%). The *picrate* separated from alcohol in yellow needles, m. p. 145° (Found: N, 18·3. $C_{10}H_{10}N_2,C_6H_3O_7N_3$ requires N, 18·1%).

1-*Phenyliminazole* (XVII; R = H).—Prepared in the same way from oxazole-4-carboxylic acid, this *base* distilled as a colourless oil at 142°/15 mm. (Found: N, 19·4. $C_9H_8N_2$ requires N, 19·4%). The *picrate* separated from alcohol in fine yellow needles, which rapidly changed to stout prisms, m. p. 155—156° (Found: N, 19·0. $C_9H_8N_2,C_6H_3O_7N_3$ requires N, 18·8%).

Ethyl 2-*Methyliminazole*-4-*carboxylate*-1-*acetate* (XVIII).—The potassium salt (VIII) (1·1 g.) was dissolved in a little alcohol and treated with glycine ethyl ester hydrochloride (0·75 g.). After 5 hours water and ether were added. The aqueous layer was extracted twice with fresh ether. Removal of the ether left a residue which soon crystallised. It was purified by solution in dilute acid and removal of neutral impurities with ether. Recovered in the usual way, the iminazole *ester* crystallised from water in matted, colourless hairy needles, m. p. 126—127° (Found, after drying at 60° in a vacuum: C, 54·7; H, 6·6; N, 12·0. $C_{11}H_{16}O_4N_2$ requires C, 55·0; H, 6·7; N, 11·7%).

Our thanks are due to the Medical Research Council for grants, and to Professor Sir Robert Robinson for valuable advice.

Dyson Perrins Laboratory, Oxford. [*Received, May 15th,* 1946.]

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25. *Reduction by Dissolving Metals. Part IV.*

By Arthur J. Birch.

Sodium in liquid ammonia dealkylates a number of aryl alkyl ethers, the ease of reaction depending on the substitution of both groups. Several catechol derivatives, including the *cyclo*hexanone acetal, substituted methylenedioxybenzenes and guaiacol methoxymethyl ether, lose an oxygen from the nucleus, giving phenol or its derivatives. Reduction of 1 : 2-, 1 : 3- and 1 : 4-dimethoxybenzene with sodium and alcohol in ammonia gives the dihydro-derivatives, together with dihydroanisoles in the case of the 1 : 2-compounds.

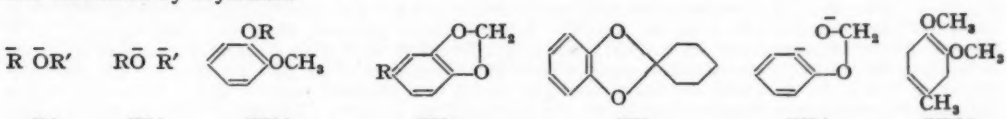
In Part I (*J.*, 1944, 430) it was shown that sodium in liquid ammonia has a demethylating action on *m*-tolyl methyl ether (*cf.* Freudenberg, Lautsch, and Piazolo, *Ber.*, 1941, **74**, 1886), the addition of alcohol being necessary for reduction of the ring. The relative ease of dealkylation of various phenol ethers by this process has now been studied and the results are consistent with the hypothesis that reaction occurs through a transition state which may be represented by (I, R = alkyl, R′ = aryl). This is supported by a comparison of the reaction rates with the effects of substituents on the stabilities of the negative charges in both the anions.

Under standard conditions the following comparative yields of monophenolic product were obtained: anisole 27%; tolyl methyl ethers, *o*- 17%, *m*- 9%, *p*- 4%; dimethoxybenzenes,

* Most m. p's. in the literature are slightly lower than this, but a Swiss patent (*Chem. Zentr.*, 1938, I, 3698) gives m. p. 144·5—145·5°.

1 : 2- 89%, 1 : 3- 71%, 1 : 4- 2·5%. 3 : 4-Dimethoxytoluene gave 4-methoxy-*m*-cresol. The order of activating influence is thus *o*-methoxyl > *m*-methoxyl > hydrogen > *o*-methyl > *m*-methyl > *p*-methyl > *p*-methoxyl. In the similar fission of unsymmetrically substituted diphenyl ethers (Sowa *et al.*, *J. Amer. Chem. Soc.*, 1937, **59**, 603, 1488; 1938, **60**, 94) where the two possible transition states may be represented by (I) and (II) (R and R′ = substituted phenyl) the one which is favoured appears to be determined by the relative substitutions of the aryl anions (R and R′ respectively) rather than the phenoxide ions—as is to be expected from the higher energy required by the former—and the substituents have the same order of activating influence as above. This must therefore express the relative effects of the groups on the stability of a negative charge either on a ring carbon atom or an oxygen atom attached to it. The full significance of this conclusion, particularly the stabilising effect of *o*-methoxyl, will be discussed later in connection with the theory of ring reduction and metallation.

The consequence of altering R in (I, R = alkyl, R′ = aryl) was determined by an examination of several guaiacol ethers (III) which gave catechol monoalkyl ethers, the ease of removal of R being in the order $CH_2Ph, CH_2{\cdot}CO_2H > CH_3 > n\text{-}C_3H_7, iso\text{-}C_3H_7$; resorcinol methyl amyl ether (m-n-*amyloxyanisole*) gave resorcinol amyl ether. These results are in accord with the theory, since the more stable the charge on R the greater the ease of formation of (I), and it has been pointed out (Part II, *J.*, 1945, 809) that charge stability is decreased by alkylation and increased by arylation.



(I.) (II.) (III.) (IV.) (V.) (VI.) (VII.)

Methylenedioxybenzene (IV, R = H), 3 : 4-methylenedioxytoluene (IV, R = CH_3), and safrole (IV, R = $CH_2{\cdot}CH{:}CH_2$) gave with sodium and alcohol in liquid ammonia phenol, *p*-cresol, and *p*-allylphenol, respectively. The same products were obtained in absence of alcohol, except that the last compound was partly isomerised to *p*-propenylphenol. The catechol acetal of *cyclo*hexanone (V) gave phenol and *cyclo*hexanol. Freudenberg, Klinck, Flickinger, and Sobek (*Ber.*, 1939, **72**, 226) have observed the formation of *p*-propylphenol from (IV, R = $n\text{-}C_3H_7$) and *m*-hydroxybenzoic acid from (IV, R = CO_2H) by the action of potassium in ammonia. All these results are explicable by assumption of an initial transition state of type (VI) where the negative charge on the aromatic ring is produced para- to the group more capable of stabilising it (H, rather than alkyl; CO_2H rather than H). Similarly with compounds of type (IV, R = CH:CHMe) the occurrence of oxygen removal (in this case para-) by means of sodium and alcohol is dependent on the presence of the conjugated double bond (Salway, *J.*, 1910, **97**, 2413), which must therefore exert a stabilising influence on a negative charge in the ring, and this is naturally greater in the para- than in the meta-position.

A similar fission of the methylenedioxy-ring has been observed when using Raney's aluminium–nickel alloy and aqueous alkali (Papa and Schwenk, *J. Org. Chem.*, 1945, **10**, 232), but in this case the isolation of *m*-cresol was claimed from both (IV, R = CHO) and (IV, R = CH_3). The former result has been confirmed, and is explicable if the ring is broken before reduction of the aldehyde group; in the latter case the product is, however, chiefly *p*-cresol, and the result therefore accords with a theory of electron addition, although it is possible that adsorption on the nickel plays some part.

The methoxymethyl ether of guaiacol (III, R = $CH_2{\cdot}OMe$), which has some similar structural features to the methylenedioxy-compounds, also lost oxygen from the ring by the action of sodium and ammonia, giving anisole.

As already noted, veratrole (III, R = Me) with sodium in ammonia gave guaiacol, but in presence of added alcohol the reaction took a different course (cf. Part I, *loc. cit.*), the products being a mixture of 2 : 5-dihydroanisole and a dihydroveratrole, probably the 3 : 6-, the latter giving on acid hydrolysis a mixture of phenol and anisole, and on treatment with 2 : 4-dinitrophenylhydrazine a derivative which is probably 2-*methoxy*-Δ^4-cyclo*hexenone* 2 : 4-*dinitrophenylhydrazone*. 4-Methylveratrole gave a mixture of a dihydro-derivative, probably the 3 : 6- (VII), and dihydro-*p*-tolyl methyl ether. The loss of oxygen is probably due chiefly to direct removal of a methoxyl from the benzene ring in the expected *m*-position to the methyl, followed by reduction of the ring, and may be compared with the loss of a methoxyl from pyrogallol ethers by reduction with sodium and alcohol (Thoms and Siebeling, *Ber.*, 1911, **44**, 2135; Semmler, *Ber.*, 1908, **41**, 2556), the methoxyl here being activated by two others. Although

(VII) also lost a methoxyl by the action of sodium in ammonia the product was chiefly dihydro-*m*-tolyl methyl ether, and the process must be a direct reduction, since preliminary bond migration would result in a tetrahydro- rather than a dihydro-benzene derivative (Part III, *J.*, 1946, 593; unpublished work).

The dimethyl ethers of resorcinol and quinol were reduced normally with sodium and alcohol in ammonia with formation of dihydro-derivatives, hydrolysed by acid to dihydroresorcinol and 1 : 4-diketo*cyclo*hexane, and reduced by further action of sodium in ammonia to the enol methyl ether of *cyclo*hexanone. Pyrogallol trimethyl ether lost a methoxyl group, since hydrolysis of the product gave dihydroresorcinol.

Experimental.

Demethylation under Standard Conditions.—The substance (0·083 g.-mol.) in ether (15 c.c.) was added to ammonia (150 c.c.) containing sodium (0·3 g.-mol.), stirring continued for 15 minutes, and the mixture left in a Dewar flask for 7 hours. It was worked up by adding crushed ice (about 75 g.) as rapidly as was safe, the oil extracted with ether, and the ammonia boiled from the aqueous solution, which was then acidified. The phenol was extracted with ether (4 × 50 c.c.), the solution dried, the ether removed, and the phenol distilled except in the case of quinol dimethyl ether where the amount was too small. The glycollic acids were prepared in the standard manner with chloroacetic acid and sodium hydroxide. Anisole gave phenol, 27%; b. p. 177—180°, m. p. 40°; *o*-tolyl methyl ether gave *o*-cresol, 17%, b. p. 190—195°, derived glycollic acid, m. p. 152°; *m*-tolyl methyl ether gave *m*-cresol, 9%, b. p. 195—200°, derived glycollic acid, m. p. 102°; *p*-tolyl methyl ether gave *p*-cresol, 4%, b. p. 195—200°, derived glycollic acid, m. p. 136°; veratrole gave guaiacol, 89%, b. p. 90°/12 mm., m. p. 27—30°, 3 : 5-dinitrobenzoate, m. p. 139°; resorcinol dimethyl ether gave resorcinol monomethyl ether, 71%, b. p. 95°/11 mm., glycollic acid, m. p. 115—116° (Gilbody, Perkin, and Yates, *J.*, 1901, **79**, 1410, give m. p. 115—118°); quinol dimethyl ether gave 2·5% of a phenolic product which did not crystallise but gave *p*-methoxyphenoxyacetic acid, m. p. and mixed m. p. 107°. The small yield in the last case may be due partly to low solubility, but it is sufficiently soluble to undergo nuclear reduction (see below).

The following were reduced by dissolving the substance (6 g.) and sodium (3 g.) in ammonia (100 c.c.), leaving the mixture in a Dewar flask for 4 hours, working it up as above. 4-Methylveratrole gave 3-hydroxy-4-methoxytoluene (4·7 g.), b. p. 100—103°/11 mm., m. p. 33° (Found: C, 69·4; H, 7·5. Calc. for $C_8H_{10}O_2$: C, 69·5; H, 7·2%). Guaiacol *n*-propyl ether (Cahours, *Compt. rend.*, 1877, **84**, 1195) gave catechol *n*-propyl ether (2·5 g.) as a viscous oil, b. p. 95—105°/9 mm., which may contain a little guaiacol (Found: C, 70·3; H, 8·0. Calc. for $C_9H_{12}O_2$: C, 71·1; H, 7·9%). Guaiacol *iso*propyl ether (Allan and Robinson, *J.*, 1926, 381), b. p. 98—100°/12 mm., gave *catechol* iso*propyl ether*, b. p. 100—102°/11 mm. (Found: C, 70·5; H, 7·8. $C_9H_{12}O_2$ requires C, 71·1; H, 7·9%). Guaiacol benzyl ether, b. p. 175°/11 mm., m. p. 58—59° after crystallisation from alcohol (Claisen, *Annalen*, 1925, **442**, 244, gives m. p. 62°) (Found: C, 78·4; H, 6·5. Calc. for $C_{14}H_{14}O_2$: C, 78·5; H, 6·5%), gave guaiacol (1·5 g.) b. p. 85—90°/11 mm., m. p. 26—28°, and a neutral fraction consisting of toluene (0·3 g.) and dibenzyl (0·6 g.), m. p. 51°, undepressed by an authentic specimen. 2-Methoxyphenoxyacetic acid, m. p. 119°, gave guaiacol (2·4 g.), b. p. 90°/11 mm., 3 : 5-dinitrobenzoate, m. p. 140°. m-n-*Amyloxyanisole* (resorcinol methyl amyl ether), prepared by the action of *n*-amyl bromide on the sodium salt of 3-methoxyphenol in boiling alcohol as a colourless oil, b. p. 140°/11 mm. (Found: C, 74·3; H, 9·2. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%), gave resorcinol amyl ether (1·4 g.), b. p. 155—160°/11 mm., which gave rise to 3-*amyloxyphenoxyacetic acid* as colourless needles from ethyl acetate–light petroleum, m. p. 95° (Found: C, 65·6; H, 7·6. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·5%).

Methylenedioxybenzene, 3 : 4-Methylenedioxytoluene, Piperonal, and Safrole.—(A) To methylenedioxybenzene (7 g.) in ammonia (150 c.c.) and alcohol (10 g.) was added sodium (5 g.) in small pieces. The product (4·1 g.) was phenol. 3 : 4-Methylenedioxytoluene (prepared by methylenation of homocatechol, Baker, *J.*, 1931, 1765) similarly gave *p*-cresol, identified as *p*-tolyloxyacetic acid, m. p. 134—136°, undepressed by an authentic specimen, m. p. 135—136°. The same products were obtained in both cases if the alcohol was omitted, but safrole in presence of alcohol gave *p*-allylphenol, b. p. 113—115°/9 mm., 3 : 5-dinitrobenzoate, m. p. 97°, and in absence of alcohol an admixture of this with *p*-propenylphenol, m. p. 93° (from alcohol) (Found: C, 80·4; H, 7·5. Calc. for $C_9H_{10}O$: C, 80·6; H, 7·4%). Both these substances on methylation and oxidation with potassium permanganate in acetone gave *p*-methoxybenzoic acid, m. p. and mixed m. p. 180—181°.

(B) 3 : 4-Methylenedioxytoluene (4 g.) was reduced with Raney's alloy (30 g.) in aqueous sodium hydroxide (200 c.c., 10%) and alcohol (100 c.c.) (cf. Papa and Schwenk, *loc. cit.*) and gave *p*-cresol (0·7 g.), identified by conversion into *p*-tolyloxyacetic acid, m. p. 132—134°, undepressed by an authentic specimen, m. p. 135—136°. Methylenedioxybenzene similarly gave phenol. Piperonal (5 g.) by the same process gave a phenolic fraction, b. p. 190—200° (2·9 g.), which on treatment with sodium hydroxide and chloroacetic acid gave a derivative, m. p. 85—95°, undepressed by *m*-tolyloxyacetic acid, m. p. 102°. After six crystallisations from water the small amount of material remaining had m. p. 127—130°, undepressed by *p*-tolyloxyacetic acid, m. p. 135—136°. The phenol was probably a mixture of *m*- and *p*-cresol with the former predominating. Methylation and reduction with sodium and alcohol in liquid ammonia followed by acid hydrolysis gave a ketone, the 2 : 4-dinitrophenylhydrazone of which had m. p. 172—174° and the semicarbazone m. p. 200—202°, both undepressed by authentic derivatives of 3-methyl-Δ^2-*cyclo*hexenone.

Attempted reduction with Raney's alloy gave only a trace of phenolic product from safrole.

cyclo*Hexanone Catechol Acetal.*—Catechol (10 g.), *cyclo*hexanone (10 g.), benzene (40 c.c.), and sulphuric acid (3 drops) were heated under reflux for 2 hours, the water formed being removed by slow distillation of the solvent. The mixture was then poured into aqueous sodium hydroxide, and the oil

extracted with ether and distilled (8 g.), b. p. 125°/10 mm., m. p. 47° from aqueous alcohol (Slooff, *Rec. Trav. chim.*, 1935, **54**, 999, gives m. p. 41°) (Found: C, 75·8; H, 7·6. Calc. for $C_{12}H_{14}O_2$: C, 75·8; H, 7·4%). This substance (5·5 g.) and sodium (3 g.) in ammonia (150 c.c.) were left for 10 hours, and worked up as usual. The neutral material (2·0 g.), b. p. 160°, was *cyclo*hexanol (3 : 5-dinitrobenzoate, m. p. 110°), and the phenolic product phenol (2·2 g.), giving phenoxyacetic acid, m. p. 98°.

Guaiacol Methoxymethyl Ether.—This was prepared in 26% yield by refluxing the sodium salt of guaiacol (1 mol.) with chloromethyl ether (1 mol.) in ether for 1 hour and direct distillation, finally under reduced pressure; b. p. 113—115°/11 mm. (cf. Hoering and Baum, D.-R.P., 1907, 209,608). This substance (6 g.) in ether (15 c.c.) was added to ammonia (80 c.c.), and sodium (2·8 g.) added in small pieces until a permanent blue was obtained. Worked up as usual, the neutral oil (2·8 g.), b. p. 40°/11 mm., $n_D^{18°}$ 1·5204, was anisole, identified by demethylation to phenol (phenoxyacetic acid, m. p. 98°). The phenolic fraction (0·4 g.) was chiefly guaiacol.

Veratrole.—Veratrole (17 g.) in alcohol (25 g.) and ammonia (250 c.c.) was reduced with sodium (9 g.). The product gave (i) b. p. 30—60°/10 mm. (5·1 g.), and (ii) b. p. 60—85°/10 mm. Fraction (i) was chiefly 2 : 5-dihydroanisole, since it gave in good yield Δ^3-*cyclo*hexenone 2 : 4-dinitrophenylhydrazone, m. p. 133°; fraction (ii) was redistilled, giving (*a*) b. p. 72—76°/10 mm. (3·6 g.), and (*b*) b. p. 83—85°/10 mm. Fraction (*a*) was 3 : 6-*dihydroveratrole* (Found: C, 68·9; H, 8·6. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%). On treatment with cold alcoholic 2 : 4-dinitrophenylhydrazine sulphate it gave 2-*methoxy*-Δ^4-cyclo*hexenone* 2 : 4-*dinitrophenylhydrazone* as red prisms from ethyl acetate–alcohol, m. p. 187—188° (Found: C, 51·0; H, 4·5. $C_{13}H_{14}O_5N_4$ requires C, 51·0; H, 4·6%). Fraction (*b*) was unchanged veratrole. 3 : 6-Dihydroveratrole (3 g.) and sodium (1·5 g.) in ammonia (35 c.c.) for 1 hour gave 2 : 5-dihydroanisole, b. p. 155—160° (1·2 g.), identified by conversion into Δ^3-*cyclo*hexenone 2 : 4-dinitrophenylhydrazone, m. p. 133°.

4-*Methylveratrole.*—This substance (18 g.) in alcohol (55 g.) and ammonia (400 c.c.) was reduced with sodium (18 g.). The product gave two main fractions: (i) b. p. 68—73°/14 mm., and (ii) b. p. 83—85°/14 mm. (7·5 g.). The former must be chiefly 2 : 5-dihydro-*p*-tolyl methyl ether, since hydrolysis with dilute acid gave a ketone, 2 : 4-dinitrophenylhydrazone, m. p. 122°, undepressed by the derivative of 4-methyl-Δ^3-*cyclo*hexenone, and converted by boiling with alcoholic sulphuric acid to the derivative of 4-methyl-Δ^2-*cyclo*hexenone, m. p. 174°, undepressed by an authentic specimen. Fraction (ii) was 4-*methyl*-3 : 6-*dihydroveratrole* (Found: C, 70·1; H, 9·1. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1%). After this (2·3 g.) had been refluxed with 10% hydrochloric acid (5 c.c.), it gave a phenolic fraction (0·8 g.), b. p. 190—200°, which is probably a mixture of *m*- and *p*-cresol since it gave a glycollic acid, m. p. 85—110°, which after several crystallisations from water gave *p*-tolyloxyacetic acid, m. p. 134—136°, undepressed by an authentic specimen. The neutral product (0·6 g.), b. p. 175—180°, appears to be a mixture of *p*- and *m*-tolyl methyl ether. Addition of 4-methyl-3 : 6-dihydroveratrole (5 g.) to sodium 4 g.) in ammonia (100 c.c.) gave some low-boiling product, apparently a hydrocarbon, and a fraction b. p. 60°/12 mm. (1·8 g.) (Found: C, 77·4; H, 9·5. Calc. for $C_8H_{12}O$: C, 77·4; H, 9·7%), which must be 2 : 5-dihydro-*m*-tolyl methyl ether, since after hydrolysis with dilute hydrochloric acid it gave 3-methyl-Δ^2-*cyclo*hexenone, semicarbazone m. p. and mixed m. p. 200—201°.

Quinol Dimethyl Ether.—This substance (13 g.) in alcohol (25 g.) and ether (40 c.c.) was added to ammonia (250 c.c.) and reduced with sodium (12 g.). The product (12 g.), 2 : 5-*dihydroquinol dimethyl ether*, b. p. 78°/12 mm., recrystallised from light petroleum (b. p. 40—60°) as colourless prisms, m. p. 54° (Found: C, 68·7; H, 8·5. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%). Refluxing with 10% hydrochloric acid for an hour, followed by chloroform extraction and recrystallisation from ethyl acetate–light petroleum gave 1 : 4-diketo*cyclo*hexane as long colourless prisms, m. p. 78°. The dihydro-ether (5 g.) and sodium (3 g.) in ammonia (50 c.c.) for two hours gave Δ^1-cyclo*hexene methyl ether*, b. p. 40°/14 mm. (2·4 g.) (Found: C, 75·4; H, 10·7. $C_7H_{12}O$ requires C, 75·0; H, 10·7%), identified by conversion into *cyclo*hexanone 2 : 4-dinitrophenylhydrazone, m. p. 161°.

Resorcinol Dimethyl Ether.—Reduced as for quinol dimethyl ether, this substance gave 2 : 5-*dihydroresorcinol dimethyl ether* (12 g.), b. p. 95°/18 mm. (Found: C, 68·6; H, 8·5. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%). This was hydrolysed by heating on the steam-bath with an equal volume of water containing a few drops of hydrochloric acid for 45 minutes, and finally in an open vessel to remove methyl alcohol. The residue was taken up in chloroform, dried, the solvent removed, and the solid crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as large colourless prisms, m. p. 105°, undepressed by an authentic specimen of dihydroresorcinol. The dihydro-ether (5 g.) further reduced with sodium as for dihydroquinol dimethyl ether, gave *cyclo*hexanone enol methyl ether, b. p. 36°/12 mm., converted into *cyclo*hexanone 2 : 4-dinitrophenylhydrazone, m. p. 162°. Pyrogallol trimethyl ether, reduced as for quinol dimethyl ether, gave an oil, b. p. 85—90°/13 mm., which on hydrolysis with hot dilute hydrochloric acid gave dihydroresorcinol, m. p. and mixed m. p. 105°.

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DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, May 18th,* 1946.

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26. *Solvent Quenching of Fluorescence.*

By E. J. BOWEN and E. COATES.

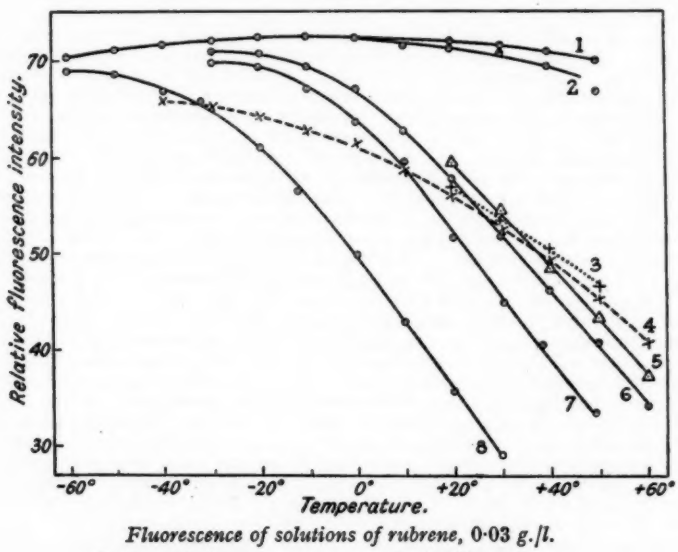
Experiments are described of the effect of temperature on the fluorescence of solutions of rubrene, naphthacene, and anthracene in various solvents. It is concluded that " dispersion force " complexes play an important part in fluorescence quenching, and that when they are

of long life they act as "inner filters"; this effect differing from other types of quenching by its negative temperature coefficient.

THIS paper describes experiments on the effect of temperature on the fluorescence of solutions of aromatic hydrocarbons in various solvents, made with the aim of throwing light on the problem of quenching by solvent molecules.

The apparatus used consisted of a small, clear Dewar vessel to contain the solution, with an internal closed metal tube for the reception of heating or cooling devices. Below this tube a concentrated, filtered beam of exciting light passed through the liquid, and at right angles to this direction the fluorescence, after passing another filter, was measured by means of a potassium photo-cell with electrometer-valve amplification. It was found that for a light absorption of about 20% the observed fluorescence was a maximum and practically independent of concentration, owing to the rise of total fluorescence with increasing concentration being balanced by the geometric factors of the proportion of the fluorescent light collected by the photo-cell. This occurred at concentrations of about 0·03 g./l., well below those where effects of concentration quenching are evident. All experiments were carried out at this concentration.

FIG. 1.



Fluorescence of solutions of rubrene, 0·03 g./l.

1. *In* cyclo*hexane.*
2. *In* n-*hexane.*
3. *In benzene.*
4. *In toluene.*
5. *In dioxan.*
6. *In* n-*butyl alcohol.*
7. *In ethyl alcohol.*
8. *In acetone.*

As fluorescent hydrocarbons, rubrene, naphthacene, and anthracene were used with the following light sources and filters:

Hydrocarbon.	Light source, filter, and wave-length.	Filter for fluorescence.
Rubrene	Filament projection lamp with 1 cm. of satd. $Cu(NO_3)_2$; 4700—5400 A.	Ilford 201
Naphthacene	Mercury lamp with ammoniacal $CuSO_4$ and acidified ferric alum filters; 4050 and 4360 A.	Ilford 108
Anthracene	Mercury lamp with Chance's OX glass; 3650 A.	Ilford 805

The solutions were cooled with liquid oxygen and heated by a nichrome spiral in the metal tube, stirring and oxygen removal being performed by a fine stream of dry hydrogen or nitrogen. Dry air was caused to circulate over the outside of the Dewar vessel to prevent moisture condensing at low temperatures.

Fig. 1 shows the results for solutions of rubrene in various solvents. It is apparent that in hexane and *cyclo*hexane the fluorescence varies little over the temperature range, and there is reason to think that the actual efficiency is near unity (Bowen and Norton, *Trans. Faraday*

Soc., 1939, **35**, 44). In the other solvents the fluorescence diminishes as the temperature is raised. As a simple scheme we may write:

		Rate.
(1)	$A + h\nu \longrightarrow A^*$	1
(2)	$A^* \longrightarrow A + h\nu'$	$k_1[A^*]$
(3)	$A^* + (S) \longrightarrow A + (S)$	$k_2[A^*]e^{-E/RT}$ since S is constant.

where E is the heat of activation of the quenching process.

If F_0 represents the fluorescence without and F the fluorescence with quenching, then

$$\log_{10}(F_0 - F)/F = \log_{10} k_2/k_1 - E/2{\cdot}3RT$$

Using the data of Fig. 1, we obtain

Solvent.	$\log_{10} k_2/k_1$.	E (k.-cals./mole).	Solvent.	$\log_{10} k_2/k_1$.	E (k.-cals./mole).
Acetone	4·7	6·46	*n*-Butyl alcohol ...	4·7	7·15
Alcohol	4·74	6·94	Dioxan	4·72	7 28

The fluorescence in these solvents tends to the hexane value at low temperatures. This is not so, however, for the solvents benzene and toluene, where the limiting value is less and the curves fall off less steeply with temperature. These flat aromatic molecules probably form "dispersion force" van der Waals complexes of unusual stability with the fluorescent molecules (see Bowen, "The Chemical Aspects of Light", 2nd edition, Clarendon Press, 1946, p. 167). These complexes are less stable than those with nitro-compounds (Briegleb, *Z. physikal. Chem.*, 1936, **32**, 305) or dye polymers (Vickerstaff and Lemin, *Nature*, 1946, **157**, 373) and affect the extinction coefficients of the solution only slightly, but we may assume that the absorbed light is divided between free and combined fluorescent molecules and that only the former fluoresce. The reaction scheme as so modified is:

		Rate.
(4)	$A + h\nu \longrightarrow A^*$	[A]/([A] + [AS])
(5)	$AS + h\nu \longrightarrow AS$	[AS]/([A] + [AS])
(6)	$A^* \longrightarrow A + h\nu'$	$k_1[A^*]$
(7)	$A^* + (S) \longrightarrow A + (S)$	$k_2[A^*]e^{-E/RT}$
(8)	$A + S \rightleftharpoons AS$	$k_3\, e^{Q/RT}[A][S] = k_4[AS]$

Whence $F_0/F = (1 + k_3\, e^{Q/RT}/k_4)(1 + k_2\, e^{-E/RT}/k_1)$.

The terms of the expression vary in opposite senses with temperature, and at low temperatures F_0/F does not rise to unity.

Experiments on naphthacene show the likelihood of this explanation. Naphthacene is a very insoluble hydrocarbon and its fluorescence could not be measured over a wide temperature range.

Fig. 2 shows results for the fluorescence of naphthacene in several solvents, including xylene with additions of 40 g./l. of naphthalene, diphenyl, and benzophenone. The effect of these added flat aromatic molecules on the fluorescence is qualitatively just as would be expected on the hypothesis of the formation of non- or feebly fluorescent complexes. A similar effect of these substances on the fluorescence of rubrene was also observed (cf. Sambursky and Wolfsohn, *Nature*, 1946, **157**, 228).

The influence of van der Waals forces on quenching is shown by the fluorescence of rubrene in mixtures of chloroform and acetone as depicted in Fig. 3. This pair of liquids is well known to give a minimum in the vapour pressure–composition curve. The minimum is due to the geometry of these molecules whereby they fit together closely so that van der Waals forces are more satisfied than in either of the pure components. There is thus less van der Waals force left over for the solute rubrene in the mixture, and, as expected, the fluorescence curves show maxima, more marked the lower the temperature.

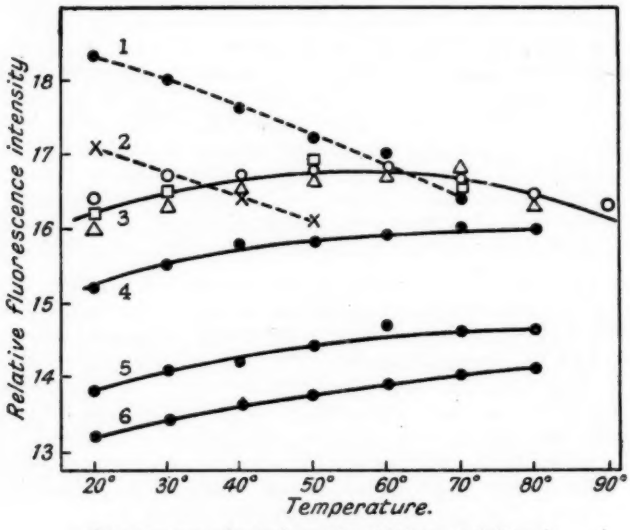
From the results of experiments on the fluorescence of rubrene in hexane, with additions of toluene as quencher, values of k_3 were obtained for van der Waals quenching by toluene. These are of the order of 0·012 and, allowing for this, the values of E and $\log_{10} k_2/k_1$ for toluene solutions of rubrene are in good agreement with those for other solvents: $E = 7{\cdot}62$ k.-cals./mole; $\log_{10} k_2/k_1 = 4{\cdot}7$.

The fluorescence efficiency of naphthacene solutions is very low, probably about 0·1, and "internal quenching" processes besides "solvent quenching" are probably operative.

The fluorescence efficiency of anthracene solutions is also less than unity (*Trans. Faraday*

Soc., 1937, **33**, 1425; 1939, **35**, 765) and some experiments were made on the effect of temperature. In benzene solution the fluorescence falls off above ordinary temperatures while in toluene it is almost temperature-independent even to low temperatures. Evidently the com-

FIG. 2.

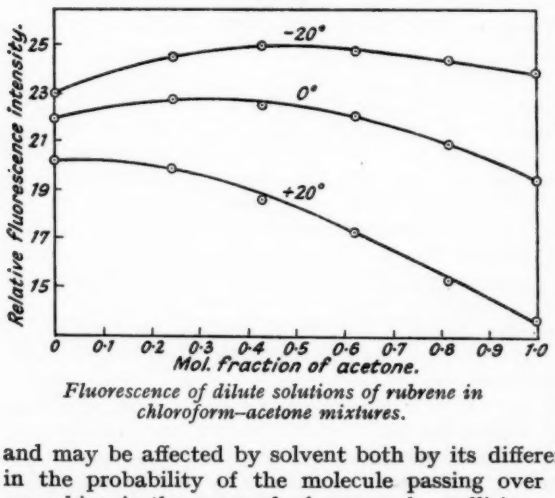


Fluorescence of solutions of naphthacene, 0·03 g./l.

1. *In xylene–ethyl alcohol mixture, 50% by vol.*
2. *In xylene–acetone mixture, 50% by vol.*
3. ○ *In xylene;* □ *in benzene;* △ *in toluene.*
4. *In xylene containing diphenyl, 40 g./l.*
5. *In xylene containing benzophenone, 40 g./l.*
6. *In xylene containing naphthalene, 40 g./l.*

plexes are less readily dissociated by heat in the latter solvent. The fluorescence in hexane solution increases at low temperatures, and this must be due to other effects than " solvent quenching " of the type discussed above.

FIG. 3.



Fluorescence of dilute solutions of rubrene in chloroform–acetone mixtures.

The measurements described above indicate that a distinction must be drawn between quenching effects due to interaction of solvent or solute molecules and the fluorescent molecule *before* or *after* the latter have absorbed a light quantum. In the former case the quenching is of the nature of an " inner filter " effect of the complexes formed between molecules in their ground states. The light absorbed by the complex is degraded either by conversion to vibrational or translational energy, or by chemical reaction. In the second case there are two possibilities, " internal " or " external ". Internal quenching arises from a crossing of the potential-energy curves of the excited and ground levels of the fluorescent molecule, and may be affected by solvent both by its differential effect on the curves and by changes in the probability of the molecule passing over from one curve to the other. External quenching is the removal of energy by collision. Both may have an energy of activation as shown in reactions (3) and (7) above. Where the solvent itself may possibly act as a quencher it is not easy to distinguish between these two possibilities. However, the difference between them may not be so sharp as might appear. Both may be translated into terms

based on the hypothesis of complex formation; on the internal mechanism the complex represents the effect of solvent on the fluorescent molecule, and on the external one complex formation and collision can be related. Fluorescence quenching in liquid systems must therefore be treated rather differently from quenching in gaseous systems.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, May 6th*, 1946.]

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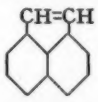
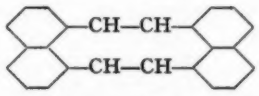
27. *The Photochemical Dimerisation of Acenaphthylene.*

By E. J. BOWEN and J. D. F. MARSH.

The quantum efficiencies of the photodimerisation of solutions of acenaphthylene in blue and near ultra-violet light have been measured at various concentrations and temperatures. The results show that the limiting efficiency is only one-tenth of that expected if all activated molecules reacted, and that the mechanism of the dimerisation is probably not of a "collisional" type, but depends on the existence of van der Waals complexes in the solution.

ORGANIC substances containing an ethylene linkage show two types of behaviour photochemically, a unimolecular *cis–trans*-change and a bimolecular dimerisation to molecules containing a *cyclo*butane ring. Though the first type has been well studied (see Olson, *J. Amer. Chem. Soc.*, **1933**, **55**, 1410; **1934**, **56**, 1320; *J. Chem. Physics*, **1933**, **1**, 418), little quantitative work has been done on the latter.

The substance chosen for this work was acenaphthylene (I) which has the advantage of being incapable of *cis–trans*-interchanges. The hydrocarbon is bright yellow, and when concentrated solutions are exposed to blue or near ultra-violet light a colourless dimeric product (II)

(I.)   (II.)

is produced, which is a mixture of two stereoisomeric forms (Dziewonski, *Ber.*, **1912**, **45**, 2491; **1913**, **46**, 1986; **1914**, **47**, 1679).

The acenaphthylene was prepared by passing acenaphthene vapour through a red-hot silica tube in a stream of carbon dioxide, and purified by fractional crystallisation of the picrate from alcohol; m. p. 93°.

Solutions of the hydrocarbon were sealed in small glass tubes of equal diameter and exposed to the light from a 500-watt mercury-vapour lamp. The tubes were kept at constant temperature by a water-bath. Under these conditions the mercury lines 4360, 4050, and 3650 A. were completely absorbed while all other lines played no part. The dimer is transparent to the first two lines but absorbs somewhat at 3650 A. and is photochemically decomposed back to the monomer, but experiments with this line removed by a filter of acidified ferric alum solution showed that the reverse reaction was negligible under our conditions of measurement. The quantum efficiency was estimated by comparison reactions with the uranyl oxalate actinometer (Leighton and Forbes, *J. Amer. Chem. Soc.*, 1930, **52**, 3139; 1934, **56**, 2363). The amount of change was found by measuring the light absorption of the solution, suitably diluted, to the mercury 4360 A. line, using a photoelectric cell. From a series of such measurements up to about 30% decomposition the initial rate of photochange for each solution was obtained. Check experiments showed that the rate was directly proportional to the light intensity and unaffected by the presence of dissolved oxygen. The table gives results for solutions in toluene, quantum efficiencies being expressed as moles of acenaphthylene removed per einstein.

Results for solutions in hexane, alcohol, and acetic acid gave figures within 20% of those for toluene.

Temp. 11°	Molarity	0·163	0·221	0·269	0·326	0·432	0·618	1·13
	Q.E.	0·012	0·017	0·018	0·021	0·028	0·038	0·059
Temp. 31°	Molarity	0·158	0·222	0·316	0·423	0·628		
	Q.E.	0·011	0·016	0·019	0·024	0·035		
Temp. 52°	Molarity	0·163	0·218	0·270	0·320	0·434	0·614	1·13
	Q.E.	0·010	0·012	0·013	0·015	0·021	0·030	0·048

The experimental figures are fitted by an expression of the form:

$$\text{Quantum efficiency} = \frac{K_1K_2[\text{A}]}{1 + K_2[\text{A}]}$$

K_1 representing the theoretical limiting value for high concentrations. The value of K_1 found is 0·18 at each temperature, instead of the value 2 which would be found if every molecule physically activated reacted to give the dimer.

Two mechanisms give the above expression :

	Rate.
$A + h\nu \longrightarrow A^*$	1
$A^* \longrightarrow A$	$(1 - a)k[A^*]$
$A^* \longrightarrow A'$	$ak[A^*]$
$A' \longrightarrow A$	$k_1[A']$
$A' + A \longrightarrow A_2$	$k_2[A'][A]$

$$\text{whence Q.E.} = \frac{2a(k_2/k_1)[A]}{1 + (k_2/k_1)[A]}$$

or	$A + A \rightleftarrows AA$	$[AA]/[A]^2 = K$
	$A + h\nu \longrightarrow A^*$	
	$AA + h\nu \longrightarrow AA^*$	$2[AA]/([A] + 2[AA])$
	$AA^* \longrightarrow AA$	$(1 - a)k[AA^*]$
	$AA^* \longrightarrow A_2$	$ak[AA^*]$
	$A^* \longrightarrow A$	

$$\text{whence Q.E.} = \frac{4aK[A]}{1 + 2K[A]}$$

The constant K_2 has a very different meaning in these two mechanisms; in the first it represents the ratio of the constants of a unimolecular deactivation process and a bimolecular dimerisation, while in the second it represents an " equilibrium constant ". The second mechanism assumes strong van der Waals " dispersion " forces between the π electrons of the aromatic molecules giving complexes AA. The interaction is assumed to be not strong enough to give marked changes in the absorption spectrum, as has been noted for the more powerful complex formation in dye solutions (Vickerstaff and Lemin, *Nature*, 1946, **157**, 373), and the absorbed light is assumed to be divided between A and AA approximately in proportion to their concentrations. The two mechanisms closely resemble those put forward by Bowen, Barnes, and Holliday (*Trans. Faraday Soc.*, 1946, to appear) to explain two types of fluorescence quenching. It is there pointed out that the first mechanism is characterised by positive temperature coefficients and the rate is inversely related to the viscosity of the medium, while in the second, viscosity plays no part and the temperature coefficient is negative. The figures of the table and the results for other solvents indicate the second mechanism for the dimerisation on these criteria. If this is so, the temperature variation of K_2 should be determined by the heat of formation of the complex AA. The value of this quantity so calculated is about 1·5 k.-cals./mole, which is comparable with other values for similar molecular interactions (cf. Bowen and Coates, preceding paper).

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, June 5th*, 1946.]

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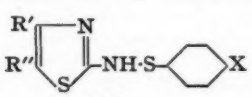
28. *The Rearrangement of 2-Benzenesulphenamidothiazoles. Part I. Thiazole Compounds not Substituted in Position 4.*

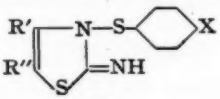
By ERIC HOGGARTH.

It is shown that a 2-benzenesulphenamidothiazole is rearranged by acetic anhyride to give a phenyl 5-thiazyl sulphide. The mechanism of the reaction and its limitations are discussed.

IT has been assumed that benzenesulphenyl halides react with 2-aminothiazoles to give as a rule the 2-benzenesulphenamides (I) and that when two isomeric compounds are formed as in the particular case of *p*-nitrobenzenesulphenyl chloride and 2-amino-4-methylthiazole, the second is a 3-sulphenamido-2-iminothiazole (II) (Wheeler, Bann, Krug, Taylor, and Gladding, B.PP. 551,681, 559,384, 559,385). Further, acetyl derivatives, presumed to correspond to these structures, have been described, and that corresponding to (II) (*i.e.* III; X = NO_2, R′ = Me, R″ = H) was obtained by the acetylation of (I) or (II) with hot acetic anhydride and by condensation of *p*-nitrobenzenesulphenyl chloride with 2-acetamido-4-methylthiazole. This formul-

ation has been challenged by Bambas (*J. Amer. Chem. Soc.*, 1945, **67**, 671) on the grounds that the sulphenamide from *p*-nitrobenzenesulphenyl chloride and 2-methylamino-4-methylthiazole (IV) undergoes an apparently similar reaction with acetic anhydride, which it is impossible to account for in terms of structure (III). He suggested that the effect of acetic anhydride on sulphenamides of type (I) is to give 2-acetamido-derivatives of phenyl 5-thiazyl sulphides (V). Certain sulphenamides are known to undergo a similar rearrangement on heating with aromatic amines (Moore and Johnson, *J. Amer. Chem. Soc.*, 1935, **57**, 2234; 1936, **58**, 1091, 1960).


(I.)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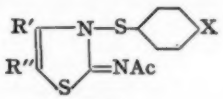
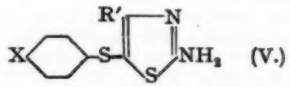

(III.)

(IV.)


(V.)

We had arrived at the same conclusion by another route. With the information contained in the patents cited above, it seemed that in order to prepare phenyl 5-thiazyl sulphides (V) it would be necessary to protect both hydrogen atoms of the 2-aminothiazole before bringing it into reaction with a sulphenyl chloride. By the intereaction of *p*-nitrobenzenesulphenyl chloride with 2-benzylideneaminothiazole followed by scission of benzaldehyde, a compound analysing correctly for (V; X = NO_2, R′ = H) was obtained. This compound on acetylation gave an acetyl derivative which proved to be identical with that obtained by the action of acetic anhydride on 2-*p*-nitrobenzenesulphenamidothiazole (I; X = NO_2, R′ = R″ = H) and by condensation of *p*-nitrobenzenesulphenyl chloride with 2-acetamidothiazole. The constitution of this compound as p-*nitrophenyl* 2-*acetamido*-5-*thiazyl sulphide* was confirmed by hydrolysis experiments. 2-*p*-Nitrobenzenesulphenamidothiazole is rapidly hydrolysed by acid to 2-aminothiazole and 4 : 4′-dinitrodiphenyl disulphide, the latter presumably arising by decomposition of the sulphenic acid first formed (cf. Zincke and Farr, *Annalen*, 1912, **391**, 57; Moore and Johnson, *loc. cit.*). Hydrolysis of the compound to which structure (III; X = NO_2, R′ = R″ = H) would be assigned by the patents cited gives a compound isomeric with the sulphenamide (I) and stable to further hydrolysis. This is of course the amino-sulphide (V; X = NO_2, R′ = H), and it is clear that a compound of formula (III) would not retain the *p*-nitrophenylthio-group on such treatment. Final proof was afforded by alternative synthesis by condensation of *p*-nitrothiophenol with 5-bromo-2-acetamidothiazole (Backer and Buisman, *Rec. Trav. chim.*, 1944, **63**, 227). The bromothiazole is not very reactive and was recovered unchanged after boiling with an alcoholic solution of *p*-nitrothiophenoxide. However, it reacted instantly with the fused thiophenol.

It was found that the rearrangement of 2-benzenesulphenamidothiazoles with acetic anhydride was by no means general. 2-p-*Chlorobenzenesulphenamido*- and 2-p-*toluenesulphenamidothiazole* (VI; X = Cl or Me) were converted by acetic anhydride even under very mild conditions into 2-acetamidothiazole and the corresponding 4 : 4′-disubstituted diphenyl disulphide. The latter possibly arises by decomposition of a mixed sulphenic-carboxylic anhydride (VII) on contact with water. Verification of the constitution of these sulphenamides was obtained by hydrolysis with acids to give 2-aminothiazole and the corresponding disulphide. The *sulphides* (V; X = Cl or Me, R′ = H) were obtained both by the action of the corresponding arylsulphenyl chloride on 2-acetamidothiazole and by condensation of 5-bromo-2-acetamidothiazole with the corresponding fused thiophenols. They were oxidised to *sulphones* by mild oxidising agents.

(VI.) (VII.)

It has been shown that the reaction of 2-*p*-nitrobenzenesulphenamidothiazole with acetic anhydride is an intermolecular rearrangement. In the presence of resorcinyl diacetate the *p*-nitrophenylthio-group substitutes almost exclusively the resorcinol molecule and no appreciable amount of thiazyl sulphide is obtained. This implies that the preliminary reaction is to split the sulphenamide linkage with subsequent attack of the 5-position of the thiazole nucleus

if the intermediate compound, perhaps (VII), is reactive enough (this depending on the aryl substituent X). Rearrangement of a 2-*p*-nitrobenzenesulphenamidothiazole will not take place if position 5 is occupied, *i.e.*, there is no tendency to attack position 4, not can compounds corresponding to the formulation (III) be isolated. 2-p-*Nitrobenzenesulphenamido-5-methylthiazole* (I; X = NO_2, R′ = H, R″ = Me) and 2-p-*nitrobenzenesulphenamido-4 : 5-dimethylthiazole* (I; X = NO_2, R′ = R″ = Me) are converted by acetic anhydride into the corresponding 2-acetamidothiazole and 4 : 4′-dinitrodiphenyl disulphide. These sulphenamides are readily hydrolysed by acid to the corresponding aminothiazole and dinitrodiphenyl disulphide.

Experimental.

p-*Nitrophenyl 2-Amino-5-thiazyl Sulphide*—(A) 2-Benzylideneaminothiazole (6·3 g.) was dissolved in hot benzene (500 c.c.), cooled to 30°, and a solution of *p*-nitrobenzenesulphenyl chloride (6·4 g.) in benzene (50 c.c.) added with stirring. After 3 hours the precipitate was collected, washed with a little light petroleum, and distilled in steam with concentrated hydrochloric acid (20 c.c.) until no more benzaldehyde was removed. The residue was diluted to 500 c.c. with hot water, filtered (charcoal), made just alkaline with sodium carbonate solution, and the solid collected and crystallised from xylene giving yellow prisms (0·8 g.), m. p. 177—178° (Found: C, 42·5; H, 2·7; S, 25·5. $C_9H_7O_2N_3S_2$ requires C, 42·7; H, 2·8; S, 25·3%). The *compound* with acetic anhydride gave an acetyl derivative which crystallised from β-ethoxyethanol in colourless prisms, m. p. 261—262° (Bambas, *loc. cit.*, gives m. p. 258—260°) (Found: C, 45·1; H, 3·05; N, 14·5. Calc. for $C_{11}H_9O_3N_3S_2$: C, 44·7; H, 3·05; N, 14·2%).

(B) 2-Aminothiazole (7·0 g.) in dry benzene (70 c.c.) was treated with a solution of *p*-nitrobenzenesulphenyl chloride (6·3 g.) in benzene (20 c.c.). After 3 hours, water (50 c.c.) was added, and the solid collected, washed with hot water, and crystallised from alcohol, giving sulphur-yellow flat needles (5·5 g.), m. p. 164° (B.P. 551,681 gives m. p. 155—160°) (Found: C, 42·4; H, 2·7; S, 25·1. Calc. for $C_9H_7O_2N_3S_2$: C, 42·7; H, 2·8; S, 25·3%). This 2-*p*-nitrobenzenesulphenamidothiazole (1·0 g.) was refluxed with concentrated hydrochloric acid (5 c.c.), alcohol (25 c.c.), and β-ethoxyethanol (10 c.c.) for 3 hours, and the solvents were evaporated under reduced pressure. The residue was treated with hot water (50 c.c.), and the insoluble powder collected and crystallised from β-ethoxyethanol giving pale yellow prisms (0·4 g.), m. p. 178—180° not depressed by 4 : 4′-dinitrodiphenyl disulphide. The aqueous filtrate was evaporated under reduced pressure, and the base liberated by concentrated sodium hydroxide solution, extracted with ether, dried (NaOH), and sublimed in a vacuum giving crystals (0·35 g.), m. p. 92—93°, not depressed by 2-aminothiazole.

2-*p*-Nitrobenzenesulphenamidothiazole (2·5 g.) was heated at 100° with acetic anhydride (15 c.c.) for 1 hour, poured into water, and the solid collected, washed with water, and crystallised from β-ethoxyethanol giving colourless prisms (1·9 g.), m. p. 260—262° not depressed by *p*-nitrophenyl 2-acetamido-5-thiazyl sulphide as prepared by the previous route (Found: C, 44·9; H, 3·5%). On hydrolysis with alcoholic hydrochloric acid this acetamido-compound (1·1 g.) gave *p*-nitrophenyl 2-amino-5-thiazyl sulphide (0·7 g.), m. p. 176—177° (Found: C, 42·4; H, 2·6%).

(C) 2-Acetamidothiazole (57·0 g.) was refluxed in dry benzene (500 c.c.) whilst a solution of *p*-nitrobenzenesulphenyl chloride (38·0 g.) in benzene (200 c.c.) was added over 10 minutes; heating was continued for 10 minutes and the solvent removed then under reduced pressure. The residue was extracted twice with boiling alcohol (1 l.) (to remove excess of 2-acetamidothiazole and small amounts of 4 : 4′-dinitrodiphenyl disulphide) and the insoluble *p*-nitrophenyl 2-acetamido-5-thiazyl sulphide crystallised from β-ethoxyethanol giving colourless prisms (33·0 g.), m. p. 260—261° (Found: C, 45·0; H, 3·4%). This compound was also obtained in excellent yield using only 1 mol. of 2-acetamidothiazole (instead of 2 as above) but it was then necessary to treat the residue, left on evaporation of the benzene, with acetic anhydride, as much deacetylation took place under these conditions. This acetamido compound was hydrolysed to *p*-nitrophenyl 2-amino-5-thiazyl sulphide, m. p. 178—179°.

(D) Dry *p*-nitrothiophenol (3·1 g.) was fused under nitrogen in an oil-bath at 160° and powdered 5-bromo-2-acetamidothiazole (4·5 g.) added with stirring. The temperature quickly rose to 210°. The reaction vessel was cooled, and the residue powdered, extracted with boiling β-ethoxyethanol (100 c.c.), filtered hot (charcoal), concentrated to 50 c.c. and allowed to crystallise. The buff powder (2·8 g.), m. p. 242—246°, was crystallised from β-ethoxyethanol giving colourless prisms, m. p. 261—262°, not depressed by *p*-nitrophenyl 2-acetamido-5-thiazyl sulphide as prepared above (Found: C, 44·9; H, 3·2%). This acetamido-compound (1·5 g.) was refluxed for 3 hours with alcohol (15 c.c.), β-ethoxyethanol (15 c.c.), and concentrated hydrochloric acid (5 c.c.), and the solvents were removed under reduced pressure. The residue was dissolved in hot water (100 c.c.), made just alkaline with sodium carbonate, and the solid collected and crystallised from xylene giving *p*-nitrophenyl 2-amino-5-thiazyl sulphide (1·1 g.), m. p. 178—179° (Found: C, 42·3; H, 3·1; S, 24·8%).

p-*Nitrophenyl 2-Amino-5-thiazyl Sulphone.*—*p*-Nitrophenyl 2-acetamido-5-thiazyl sulphide (36·0 g.) in glacial acetic acid (1 l.) was treated with a solution of potassium permanganate (60·0 g.) in water (1 l.), the temperature being allowed to rise to 30—35° but not higher. The mixture was stirred overnight, the manganese dioxide removed with sulphur dioxide, and the solid collected and crystallised from β-ethoxyethanol giving colourless prisms (28·2 g.), m. p. 275° (Bambas, *loc. cit.*, gives m. p. 274—276°) (Found: C, 40·9; H, 2·8; N, 13·4; S, 19·8. Calc. for $C_{11}H_9O_5N_3S_2$: C, 40·4; H, 2·8; N, 12·8; S, 19·6%). This acetamido-compound (22·0 g.) was hydrolysed by boiling with a saturated solution of hydrogen chloride in methyl alcohol (1 l.) for 3 hours. The solvent was removed under reduced pressure, the residue neutralised with sodium carbonate solution, and the solid collected and crystallised from alcohol giving golden yellow plates (13·5 g.), m. p. 228° (Bambas, *loc. cit.*, gives m. p. 230—232°) (Found: C, 38·3; H, 2·6; S, 22·7. Calc. for $C_9H_7O_4N_3S_2$: C, 37·9; H, 2·5; S, 22·45%).

p-*Aminophenyl* 2-*Amino-5-thiazyl Sulphone.*—*p*-Nitrophenyl 2-acetamido-5-thiazyl sulphone (10·0 g.) was reduced in a mixture of methyl alcohol (150 c.c.) and β-ethoxyethanol (350 c.c.) with Raney nickel catalyst at ordinary pressure and temperature. The liquid was filtered hot, saturated with hydrogen chloride, refluxed for 3 hours, and evaporated under reduced pressure. The residue was dissolved in water, neutralised with sodium carbonate, and the solid collected and crystallised from aqueous methyl alcohol giving colourless needles (7·7 g.), m. p. 218—219° (Bambas, *loc. cit.*, gives m p. 219—221°) (Found: C, 42·1; H, 3·45; N, 16·65; S, 24·7. Calc. for $C_9H_9O_2N_3S_2$: C, 42·4; H, 3·5; N, 16·5; S, 25·1%). The diamine was also obtained by direct catalytic reduction of *p*-nitrophenyl 2-amino-5-thiazyl sulphone.

2-p-*Toluenesulphenamidothiazole.*—*p*-Toluenesulphenyl chloride (7·9 g.) in dry benzene (100 c.c.) was added to a solution of 2-aminothiazole (10·0 g.) in benzene (300 c.c.) with stirring, water (200 c.c.) was added, and the benzene layer separated, washed twice with small amounts of water, and the solvent evaporated under reduced pressure. The residual brown oil was crystallised from light petroleum (b. p. 60—80°) giving large colourless needles (5·9 g.), m. p. 120°, discoloured by a few minutes' heating at 100° (Found: C, 54·35; H, 4·4. $C_{10}H_{10}N_2S_2$ requires C, 54·0; H, 4·5%). This *compound* (1·5 g.), concentrated hydrochloric acid (5 c.c.), and alcohol (15 c.c.) were refluxed for 2 hours, water (50 c.c.) added, and the oil extracted with benzene. The residual aqueous solution was evaporated, made alkaline with sodium hydroxide solution, and the liberated base extracted with ether, dried (NaOH), and sublimed in a vacuum giving colourless prisms (0·5 g.), m. p. 92—93°, not depressed by 2-aminothiazole. The benzene solution was evaporated and the residue distilled giving a yellow oil, b. p. 230—235°/35 mm., setting to a crystalline solid (0·55 g.), m. p. 46—47°, not depressed by 4 : 4′-ditolyl disulphide.

2-*p*-Toluenesulphenamidothiazole (3·0 g.) and acetic anhydride (10 c.c.) were heated for 5 minutes at 50° and warm water (25 c.c.) was added. The aqueous liquor was decanted from the viscous gum, heated to 80°, neutralised with solid sodium carbonate, and filtered hot with a little charcoal. On standing, colourless needles (0·9 g.), m. p. 201—202°, not depressed by 2-acetamidothiazole, separated. The residual gum was extracted hot with light petroleum (b. p. 40—60°, 50 c.c.), the extract filtered with charcoal, evaporated, and the residue distilled, giving a yellow oil, b. p. 230—238°/40 mm. (1·0 g.), setting to a crystalline solid, m. p. 45—46°, not depressed by 4 : 4′-ditolyl disulphide. This experiment was repeated using the sulphenamide (1·5 g.) and acetic anhydride (5 c.c.), but heating at 95—100° for 1 hour. Much darkening took place, but there were isolated 2-acetamidothiazole (0·35 g., m. p. 202°) and the disulphide (0·55 g., m. p. 41—42°).

2-p-*Chlorobenzenesulphenamidothiazole.*—This compound was prepared from *p*-chlorobenzenesulphenyl chloride (6·0 g.) and 2-aminothiazole (6·8 g.) as described for the *p*-toluene compound and crystallised from benzene–light petroleum (b. p. 60—80°) giving colourless glistening needles (6·2 g.), m. p. 139° (Found: Cl, 14·6; S, 26·7. $C_9H_7N_2ClS_2$ requires Cl, 14·6; S, 26·4%). This *sulphenamide* (1·5 g.) was hydrolysed as described for the *p*-toluene compound giving 2-aminothiazole (0·5 g., m. p. 90—92°) and 4 : 4′-dichlorodiphenyl disulphide (0·6 g., m. p. 74°).

2-*p*-Chlorobenzenesulphenamidothiazole (2·0 g.) and acetic anhydride (10 c.c.) were heated at 50° for 10 minutes giving 2-acetamidothiazole (0·65 g., m. p. 202°) and 4 : 4′-dichlorodiphenyl disulphide (0·8 g., m. p. 74°) isolated as described for the *p*-toluene compound. Heated at 95—100°, the sulphenamide (1·5 g.) gave 2-acetamidothiazole (0·4 g., m. p. 203°) and the disulphide (0·3 g., m. p. 74°).

Reaction of 2-p-*Nitrobenzenesulphenamidothiazole with Acetic Anhydride in the Presence of Resorcinyl Diacetate.*—The sulphenamide (2·5 g.) was added to a solution of resorcinol (2·2 g. = 2 mols.) in acetic anhydride (20 c.c.) at 90° over ½ hour, heated for ½ hour longer, and diluted with water. The solid was collected, refluxed for 3 hours with alcohol (50 c.c.) and concentrated hydrochloric acid (5·0 c.c.), poured into water, and the precipitate again collected. The yellow solid was dissolved in 10% sodium carbonate solution (100 c.c.), filtered, precipitated with acetic acid, collected, and crystallised from dilute acetic acid giving yellow needles (1·8 g.), m. p. 184°, identical with 4-nitro-2′ : 4′-dihydroxydiphenyl sulphide (Burton and Hoggarth, *J.*, 1945, 469).

p-*Tolyl* 2-*Amino-5-thiazyl Sulphide.*—(A)—2-Acetamidothiazole (14·5 g.), *p*-toluenesulphenyl chloride (16·0 g.), and benzene (500 c.c.) were refluxed for 3 hours, the solvent evaporated, and the residue refluxed for 5 minutes with acetic anhydride (50 c.c.). Water (500 c.c.) was added, and the solid collected and crystallised from alcohol giving colourless needles of p-*tolyl* 2-*acetamido-5-thiazyl sulphide* (10·8 g.), m. p. 202° (Found: C, 54·85; H, 4·45; S, 24·6. $C_{12}H_{12}ON_2S_2$ requires C, 54·5; H, 4·5; S, 24·2%). This compound (2·0 g.) was refluxed with methyl alcoholic hydrogen chloride (100 c.c.) for 6 hours, water (50 c.c.) was added, and the solvents were removed under reduced pressure. The residue was dissolved in water, made just alkaline with sodium carbonate solution, and the solid collected and crystallised from methyl alcohol giving the *amino-sulphide* in fine colourless needles (1·6 g.), m. p. 146° (Found: C, 54·1; H, 4·3. $C_{10}H_{10}N_2S_2$ requires C, 54·0; H, 4·5%).

(B) 5-Bromo-2-acetamidothiazole (4·5 g.) and thio-*p*-cresol (5·0 g.) were heated for 4 hours at 130°, cooled, the excess of the thiophenol dissolved in ether, and the residual solid crystallised from alcohol giving colourless needles of *p*-tolyl 2-acetamido-5-thiazyl sulphide (2·2 g.), m. p. 202° (Found: C, 54·8; H, 4·6, S, 24·4%). Hydrolysis with acid gave the amino-sulphide, m. p. 146°, identical with the compound prepared by the first route (Found: C, 54·4; H, 4·6; S, 28·6).

p-*Chlorophenyl* 2-*Amino-5-thiazyl Sulphide.*—(A) *p*-Chlorobenzenesulphenyl chloride (6·0 g.) and 2-acetamidothiazole (4·8 g.) gave p-*chlorophenyl* 2-*acetamido-5-thiazyl sulphide*, which crystallised from benzene in colourless needles (5·0 g.), m. p. 196° (Found: C, 46·7; H, 3·4; Cl, 12·2. $C_{11}H_9ON_2ClS_2$ requires C, 46·5; H, 3·2; Cl, 12·5%). Deacetylation gave the *amino-sulphide* which crystallised from benzene giving colourless leaflets, m. p. 172° (Found: C, 44·5; H, 3·15. $C_9H_7N_2ClS_2$ requires C, 44·5; H, 2·9%).

(B) *p*-Chlorothiophenol (4·0 g.) and 5-bromo-2-acetamidothiazole (2·3 g.) were heated for 3 hours at 155—160° and gave *p*-chlorophenyl 2-acetamido-5-thiazyl sulphide, (1·1 g.), m. p. 195—196° (Found: Cl, 12·3; S, 22·6). This was deacetylated by acid to the amino-sulphide, m. p. 172° (Found: Cl, 15·1; S, 26·6).

p-*Tolyl* 2-*Amino*-5-*thiazyl Sulphone*.—*p*-Tolyl 2-acetamido-5-thiazyl sulphide (5·3 g.) in acetic acid (90 c.c.) was oxidised by a solution of potassium permanganate (6·6 g.) in water (100 c.c.), added with stirring at 30—35°. Sulphur dioxide was passed until the manganese dioxide had dissolved, the solid collected, and the p-*tolyl* 2-*acetamido*-5-*thiazyl sulphone* crystallised from alcohol giving lustrous needles (4·1 g.), m. p. 257—258° (Found: C, 48·55; H, 4·25; S, 21·9. $C_{12}H_{12}O_3N_2S_2$ requires C, 48·6; H, 4·1; S, 21·6%). This acetamido-compound (3·0 g.) was refluxed with concentrated hydrochloric acid (25 c.c.) and β-ethoxyethanol (25 c.c.) for 2 hours, evaporated under reduced pressure, the residue dissolved in strong ammonia solution, diluted with water, made just acid with acetic acid, and the solid collected and crystallised from alcohol giving colourless needles (2·1 g.) of the *amino-sulphone*, m. p. 234° (Found: C, 47·35; H, 3·7; S, 25·8. $C_{10}H_{10}O_2N_2S_2$ requires C, 47·2; H, 3·9; S, 25·2%).

p-*Chlorophenyl* 2-*Amino*-5-*thiazyl Sulphone*.—*p*-Chlorophenyl 2-acetamido-5-thiazyl sulphide (2·8 g.) was oxidised as described for the *p*-tolyl sulphide and gave p-*chlorophenyl* 2-*acetamido*-5-*thiazyl sulphone*, which crystallised from alcohol giving a mass of felted needles (1·9 g.), m. p. 275° (Found: C, 41·95; H, 3·1; Cl, 10·9; S, 20·2. $C_{11}H_9O_3N_2ClS_2$ requires C, 41·7; H, 2·8; Cl, 11·2; S, 20·2%). This acetamido-compound (1·6 g.) was hydrolysed to the *amino-sulphone*, which crystallised from alcohol giving large clumps of colourless needles (0·9 g.), m. p. 209° (Found: C, 39·3; H, 2·6; S, 23·7. $C_9H_7O_2N_2ClS_2$ requires C, 39·3; H, 2·55; S, 23·3%).

2-p-*Nitrobenzenesulphenamido*-5-*methylthiazole*.—2-Amino-5-methylthiazole reacted with *p*-nitrobenzenesulphenyl chloride as described for 2-aminothiazole giving the *sulphenamide*, which crystallised from xylene in golden yellow plates (58% of theory), m. p. 158° (Found: C, 45·05, H, 3·4; S, 23·7. $C_{10}H_9O_2N_3S_2$ requires C, 44·9; H, 3·4; S, 24·0%). This compound (2·7 g.) was hydrolysed by acid to 4 : 4′-dinitrodiphenyl disulphide (0·9 g., m. p. 180°) and 2-amino-5-methylthiazole (1·0 g., m. p. 96—98°).

2-*p*-Nitrobenzenesulphenamido-5-methylthiazole (13·3 g.) was heated for 1 hour with acetic anhydride (70 c.c.) at 100°, the solution poured into water, and the solid collected, dried, and crystallised from toluene (300 c.c.) giving 2-acetamido-5-methylthiazole (3·5 g., m. p. 221°). The mother liquor was evaporated under reduced pressure and the residue crystallised from β-ethoxyethanol (100 c.c.) giving 4 : 4′-dinitrodiphenyl disulphide (4·4 g., m. p. 180°). The filtrate was treated with concentrated hydrochloric acid (20 c.c.), refluxed for 3 hours, diluted with water (100 c.c.), and the solid collected and crystallised from β-ethoxyethanol giving a further quantity of dinitrodiphenyl disulphide (1·7 g., m. p. 179°). The acid filtrate was evaporated under reduced pressure and basified with concentrated sodium hydroxide solution, and 2-amino-5-methylthiazole (1·8 g., m. p. 96°) was isolated by ether extraction and sublimation in a vacuum.

2-p-*Nitrobenzenesulphenamido*-4 : 5-*dimethylthiazole*.—2-Amino-4 : 5-dimethylthiazole reacted with *p*-nitrobenzenesulphenyl chloride as described for 2-aminothiazole giving the *sulphenamide*, which crystallised from xylene in golden yellow prisms (62% of theory), m. p. 166° (Found: C, 47·15; H, 3·65. $C_{11}H_{11}O_2N_3S_2$ requires C, 47·0; H, 3·9%). Hydrolysis of this compound (1·5 g.) with hydrochloric acid gave 4 : 4′-dinitrodiphenyl disulphide (0·6 g., m. p. 180°) and 2-amino-4 : 5-dimethylthiazole (0·5 g., m. p. 82°).

2-*p*-Nitrobenzenesulphenamido-4 : 5-dimethylthiazole (4·0 g.) was heated for 2 hours with acetic anhydride at 90° and the excess removed under reduced pressure. The residue was stirred with a mixture of water (50 c.c.) and alcohol (50 c.c.), filtered, and the solid crystallised from β-ethoxyethanol giving 4 : 4′-dinitrodiphenyl disulphide (1·6 g., m. p. 180°). The filtrate was evaporated and the residue crystallised from water giving 2-acetamido-4 : 5-dimethylthiazole (1·8 g., m. p. 146°).

IMPERIAL CHEMICAL INDUSTRIES LIMITED, RESEARCH LABORATORIES,
BLACKLEY, MANCHESTER, 9.

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29. *The Rearrangement of 2-Benzenesulphenamidothiazoles. Part II. Thiazole Compounds Substituted in Position 4.*

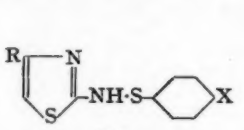
By ERIC HOGGARTH.

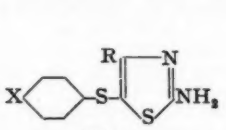
The course of the reactions discussed in Part I (preceding paper) is shown to be greatly modified by the substituent in position 4 of the thiazole ring.

IT was shown in Part I that of the 2-benzenesulphenamidothiazoles (I; X = NO_2, Me, or Cl, R = H) only the *p*-nitro-compound is converted into the acetyl derivative of the isomeric phenyl 2-amino-5-thiazyl sulphide (II) by acetic anhydride. However, when the thiazole ring carries a methyl group in position 4, all three *sulphenamides* (I; X = NO_2, Me, or Cl, R = Me) have been found to rearrange to the corresponding compounds (II) by the same treatment. Like compounds lacking the 4-methyl group, 2-acetamido-4-methylthiazole was attacked by all three benzenesulphenyl chlorides to give acetyl derivatives of compounds of type (II) directly. These acetyl derivatives were hydrolysed to the free 2-amino-compounds, identical with those obtained by condensing 5-bromo-2-amino-4-methylthiazole (Ochiai and Nagasawa, *Ber.*, 1939, **72**, 1470) with the corresponding thiophenols. Oxidation of the acetyl derivatives of the sulphides (II) followed by deacetylation gave *phenyl* 2-*amino*-4-*methyl*-5-*thiazyl sulphones*.

5-Bromo-2-amino-4-methylthiazole reacted very much more readily with thiophenols than did 5-bromo-2-acetamidothiazole. This implied the possibility that in the former bromo-

compound the bromine atom was not in the thiazole ring as has been assumed but in the methyl group; if this were so the sulphides (II) would have the isomeric structure (III). A sulphone


(I.)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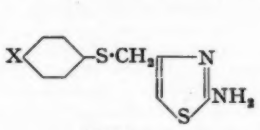
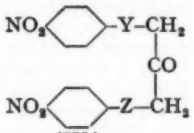

(III.)


(IV.)

corresponding to (III) was synthesised as follows. *p*-Nitrophenylsulphonylacetone (Burton and Hoggarth, *J.*, 1945, 470) was monobrominated and the constitution of the product established as 3-*bromo*-1-p-*nitrophenylsulphonylacetone* by condensation with sodium *p*-nitrothiophenoxide to give a *sulphide-sulphone* (IV; Y = S, Z = SO_2) which was oxidised to a disulphone (IV; Y = Z = SO_2) identical with 1 : 3-*bis*-p-*nitrophenylsulphonylacetone* prepared by condensation of *s*-dichloroacetone with 2 mols. of sodium *p*-nitrothiophenoxide and oxidation of the resulting 1 : 3-*bis*-p-*nitrophenylthioacetone* (IV; Y = Z = S). 3-Bromo-1-*p*-nitrophenylsulphonylacetone reacted with thiourea to give 2-*amino*-4-(p-*nitrophenylsulphonylmethyl*)-*thiazole* (II; X = NO_2); this was reduced to the *diamine* (III; X = NH_2).

When the sulphenamides (I; R = Me, X = NO_2, Me, or Cl) were treated with acid under conditions suitable for the scission of the corresponding sulphenamides lacking the methyl group (see Part I) the isomeric phenyl 2-amino-4-methyl-5-thiazyl sulphides were obtained in excellent yield. It appears therefore that the presence of the 4-methyl group activates position 5 sufficiently to make attack possible by the (assumed) intermediate sulphenic acid. It was shown that this rearrangement, like that caused by the action of acetic anhydride, is intermolecular, for in the presence of resorcinol some 4-nitro-2′ : 4′-dihydroxydiphenyl sulphide was formed. However, unlike the reaction of 2-*p*-nitrobenzenesulphenamidothiazole with acetic anhydride in the presence of resorcinyl diacetate (Part I), much of the phenyl 5-thiazyl sulphide was also isolated. The action of acids on sulphenamides of 2-amino-4-methylthiazole is very similar to the rearrangement of some *o*-nitrobenzenesulphenylphenyl esters to *o*-nitro-*p*′-hydroxydiphenyl sulphides observed by Smiles and Learmonth (*J.*, 1936, 327). Both reactions are effected by acid and are not truly intramolecular.

A small amount of *p*-nitrophenyl 2-amino-4-methyl-5-thiazyl sulphide was found as a by-product in the preparation of 2-*p*-nitrobenzenesulphenamido-4-methylthiazole, and, when the thiazole ring carried a phenyl group in place of the methyl, reaction with *p*-nitrobenzenesulphenyl chloride gave only the phenyl 5-thiazyl sulphide (II; R = Ph, X = NO_2), no sulphenamide being isolable under the usual conditions. The structure of the product was established by stability to hydrolysis with acid and recovery unchanged after acetylation followed by hydrolysis. Furthermore, oxidation of the acetyl derivative gave an *acetamidosulphone* which was hydrolysed to p-*nitrophenyl* 2-*amino*-4-*phenyl*-5-*thiazyl sulphone*, whereas 2-*p*-nitrobenzenesulphonamido-4-phenylthiazole would result from this sequence of reactions if a very stable sulphenamide were assumed to be the product of the initial reaction. An alternative synthesis has been achieved as follows. 2-Amino-4-phenylthiazole under conditions suitable for the bromination of the 4-methyl compound gave a monobromo-derivative which must be 5-*bromo*-2-*amino*-4-*phenylthiazole*, and this was condensed with sodium-*p*-nitrothiophenoxide. These results bring the reactions of benzenesulphenyl chlorides with 2-aminothiazoles into line with the corresponding reactions with simple aromatic amines. 2-Aminothiazole itself resembles aniline and *p*-toluidine in giving no appreciable amount of sulphide under the usual conditions, 2-amino-4-phenylthiazole resembles the naphthylamines in giving nuclear substitution product almost exclusively, and 2-amino-4-methylthiazole is intermediate, both sulphide and sulphenamide being formed (cf. Zincke and Lenhardt, *Annalen*, 1913, **400**, 2).

Experimental.

2-p-*Nitrobenzenesulphenamido*-4-*methylthiazole*.—A solution of *p*-nitrobenzenesulphenyl chloride (11·4 g.) in benzene (100 c.c.) was added with stirring to a solution of 2-amino-4-methylthiazole (7·0 g.) in benzene (100 c.c.) during 1 hour, and the solid collected and crystallised from xylene to give faintly yellow plates (6·8 g.), m. p. 181° (B.P. 551,681 gives m. p. 183°) (Found: C, 45·0; H, 3·6. Calc. for $C_{10}H_9O_2N_3S_2$: C, 44·9; H, 3·4%). Evaporation of the benzene mother liquors gave a sticky solid which was ground with water and extracted with hot benzene–light petroleum (b. p. 60—80°). On cooling, the extract deposited a yellow powder (0·3 g.), m. p. 160—166°, which was recrystallised from the same solvents giving a mixture of the two dimorphs of p-*nitrophenyl* 2-*amino*-4-*methyl*-5-*thiazyl sulphide* (see below), m. p. 172°, 172—173° Found: S, 24·1, 24·25. $C_{10}H_9O_2N_3S_2$ requires S, 24·0%).

p-*Nitrophenyl 2-Amino-4-methyl-5-thiazyl Sulphide.*—(A) The above sulphenamide (2·7 g.) and acetic anhydride (5 c.c.) were heated at 95° for 5 minutes, water (200 c.c.) was added, and the precipitate collected and crystallised from aqueous alcohol to give faintly yellow needles of *p*-nitrophenyl 2-acetamido-4-methyl-5-thiazyl sulphide (2·2 g.), m. p. 178—179° (B.P. 559,384 gives m. p. 183°) (Found: C, 46·5; H, 3·7; S, 20·9. Calc. for $C_{12}H_{11}O_3N_3S_2$: C, 46·6; H, 3·55; S, 20·7%). This acetamido-compound (2·0 g.) was refluxed for 3 hours with alcohol (50 c.c.) and concentrated hydrochloric acid (5 c.c.), the solvents were evaporated under reduced pressure, and the residue was treated with water (50 c.c.) and made just alkaline with sodium carbonate. The solid was collected and crystallised from benzene–light petroleum (b. p. 60—80°) giving a yellow crystalline powder (1·5 g.), m. p. 172°, which on slow recrystallisation from the same solvents gave a mixture of two *dimorphs* of the amino-sulphide; (*a*) large deep golden yellow prisms, m. p. 172—173° (Found: C, 45·25; H, 3·5%), and (*b*) clusters of pale yellow needles, m. p. 172—173° (Found: C, 45·0; H, 3·7%). There was no depression of m. p. when (*a*) and (*b*) were mixed, and crystallisation of hand-picked samples always gave mixtures.

(B) 2-Acetamido-4-methylthiazole (31·0 g.) in benzene (200 c.c.) was treated with *p*-nitrobenzene-sulphenyl chloride (19·0 g.) in benzene (100 c.c.) at 40—50°, the solvent evaporated, and the residue treated with acetic anhydride (100 c.c. at 100°), poured into water, and crystallised from aqueous alcohol giving colourless needles of the acetyl derivative (29·2 g.), m. p. 178—179°, identical with that prepared in (A) (Found: C, 46·4; H, 3·8%).

(C) 5-Bromo-2-amino-4-methylthiazole (3·8 g.) and sodium *p*-nitrothiophenoxide (3·6 g.) were refluxed in alcohol for 3 hours, water (200 c.c.) was added, and the solid collected and crystallised from benzene–light petroleum (b. p. 60—80°) giving the amino-sulphide (3·2 g.), m. p. 172—173°. On slow recrystallisation two dimorphs were formed identical with those described under (A) (Found: C, 44·7, 45·1; H, 3·7, 3·4%). Acetylation with acetic anhydride of hand-picked specimens of either dimorph gave the same acetyl derivative, m. p. 179° (Found: C, 46·4; H, 3·3; S, 20·6%).

(D) 2-*p*-Nitrobenzenesulphenamido-4-methylthiazole (2·0 g.), concentrated hydrochloric acid (10 c.c.), alcohol (50 c.c.), and β-ethoxyethanol (20 c.c.) were refluxed for 3 hours and then evaporated under reduced pressure. The residue was ground in a mortar with 10% sodium carbonate solution (50 c.c.), and the solid collected and crystallised from benzene–light petroleum (b. p. 60—80°) giving a mixture of the two dimorphic forms of the amino-sulphide (1·4 g.), m. p. 172—173°, 173° (Found: S, 24·3, 23·8%).

2-p-*Toluenesulphenamido-4-methylthiazole.*—2-Amino-4-methylthiazole (11·4 g.) in dry benzene (150 c.c.) was treated with a solution of *p*-toluenesulphenyl chloride (15·8 g.) in dry benzene (150 c.c.), added with stirring during ½ hour; the solid was collected, ground with warm water, again collected, and crystallised from ethyl acetate–alcohol giving colourless plates of 2-p-*toluenesulphenamido-4-methyl-thiazole dihydrate* (5·8 g.), m. p. 224° (Found: C, 48·3, 48·75; H, 5·5, 5·9; S, 23·9, 23·4. $C_{11}H_{13}N_3S_2,2H_2O$ requires C, 48·5; H, 5·9; S, 23·6%).

p-*Tolyl 2-Amino-4-methyl-5-thiazyl Sulphide.*—(A) The above sulphenamide (5·0 g.) and acetic anhydride (15 c.c.) were heated for 1 hour at 90°, poured into water (500 c.c.), and the solid collected and crystallised from light petroleum (b. p. 60—80°) giving colourless needles (3·1 g.), m. p. 149° (Found: C, 56·25; H, 4·65; S, 22·6. $C_{11}H_{14}ON_2S_2$ requires C, 56·2; H, 5·0; S, 22·9%). This *acetamido*-compound was hydrolysed by acid to the *amino-sulphide*, which crystallised from light petroleum (b. p. 60—80°) in fine colourless needles, m. p. 141° (Found: C, 55·6; H, 5·05. $C_{11}H_{12}N_3S_2$ requires C, 55·9; H, 5·1%).

(B) A solution of *p*-toluenesulphenyl chloride (53·0 g.) in benzene (500 c.c.) was added to a solution of 2-acetamido-4-methylthiazole (52·0 g.) in benzene (1 l.) at 45—55°, the solvent evaporated under reduced pressure, the residue heated with acetic anhydride (200 c.c.) and poured into water, and the solid collected and crystallised from light petroleum (b. p. 60—80°) giving colourless flattened needles or plates of the acetyl derivative (56·5 g.), m. p. 149° (Found: C, 55·8; H, 4·8%).

(C) 5-Bromo-2-amino-4-methylthiazole (4·0 g.) and thio-*p*-cresol (5·0 g.) were heated by an oil-bath at 120° for 1 hour; the reaction mixture was cooled, treated with water (100 c.c.) and 40% sodium hydroxide solution (10 c.c.), and the solid precipitate collected and crystallised from light petroleum (b. p. 60—80°) giving 1·1 g., m. p. 141° (Found: C, 55·5; H, 5·0; S, 26·9%). The acetyl derivative, prepared with acetic anhydride, was crystallised from light petroleum (b. p. 60—80°); m. p. 149—150° (Found: C, 55·8; H, 4·5; S, 22·8%).

(D) 2-*p*-Toluenesulphenamido-4-methylthiazole (2·0 g.), concentrated hydrochloric acid (10 c.c.), and alcohol (50 c.c.) were refluxed for 3 hours to give the amino-sulphide (1·5 g.), m. p. 142° (Found: S, 27·3%).

2-p-*Chlorobenzenesulphenamido-4-methylthiazole.*—This *compound* was prepared as described for the *p*-toluene compound from 2-amino-4-methylthiazole and *p*-chlorobenzenesulphenyl chloride (71% yield). It crystallised from alcohol–ethyl acetate in colourless prisms, m. p. 221° (Found: Cl, 13·6; S, 24·8. $C_{10}H_9N_3ClS_2$ requires Cl, 13·8; S, 25·0%).

p-*Chlorophenyl 2-Amino-4-methyl-5-thiazyl Sulphide.*—(A) The above sulphenamide (2·5 g.) was heated with acetic anhydride (10 c.c.) to give p-*chlorophenyl 2-acetamido-4-methyl-5-thiazyl sulphide*, which crystallised from benzene–light petroleum (b. p. 60—80°) in colourless prisms (1·9 g.), m. p. 152° (Found: Cl, 11·6; S, 21·5. $C_{12}H_{11}ON_3ClS_2$ requires Cl, 11·9; S, 21·4%). By hydrolysis with acid the *amino-sulphide* was obtained; this crystallised from light petroleum (b. p. 60—80°) in colourless needles (73%), m. p. 145° (Found: Cl, 13·8; S, 24·65. $C_{10}H_9N_3ClS_2$ requires Cl, 13·8; S, 25·0%).

(B) The acetyl derivative was prepared by interaction of *p*-chlorobenzenesulphenyl chloride and 2-acetamido-4-methylthiazole as described for the *p*-tolyl compound above (85% yield); m. p. 151—152° (Found: C, 48·4; H, 3·75%).

(C) 5-Bromo-2-amino-4-methylthiazole and *p*-chlorothiophenol reacted together as described for the corresponding *p*-tolyl compound to give the amino-sulphide, m. p. 144—145° (Found: C, 47·1; H, 3·75; S, 24·6%). The acetyl derivative was prepared with acetic anhydride; m. p. 151—152° (Found: C, 48·35; H, 3·7; S, 21·5%).

(D) 2-*p*-Chlorobenzenesulphenamido-4-methylthiazole (2·0 g.), concentrated hydrochloric acid (10 c.c.), and alcohol (50 c.c.) were refluxed for 3 hours to give the amino-sulphide (1·2 g.), m. p. 146° (Found : Cl, 11·7; S, 21·8%).

p-*Nitrophenyl 2-Amino-4-methyl-5-thiazyl Sulphone.*—*p*-Nitrophenyl 2-acetamido-4-methyl-5-thiazyl sulphide (13·0 g.) in acetic acid (150 c.c.) was oxidised with potassium permanganate (13·0 g.) in water (150 c.c.), sulphur dioxide passed until the brown colour was discharged, and the solid collected and crystallised from alcohol giving shining leaflets (8·8 g.), m. p. 232° (Found : C, 42·15; H, 3·05; S, 18·5. $C_{12}H_{11}O_5N_3S_2$ requires C, 42·2; H, 3·2; S, 18·8%). This *acetamido*-compound (6·5 g.) was hydrolysed by acid to the *amino-sulphone* which crystallised from β-ethoxyethanol in sulphur yellow prisms (5·2 g.), m. p. 204° (Found : C, 40·25; H, 3·1; S, 21·7. $C_{10}H_9O_4N_3S_2$ requires C, 40·1; H, 3·0; S, 21·4%).

p-*Aminophenyl 2-Amino-4-methyl-5-thiazyl Sulphone.*—This compound was obtained by catalytic reduction of the above amino-nitro-sulphone in alcohol with Raney nickel catalyst; it crystallised from water in shining leaflets, m. p. 173° (B.P. 559,385 gives m. p. 180°) (Found : C, 44·4; H, 3·9; S, 23·4. Calc. for $C_{10}H_{11}O_2N_3S_2$: C, 44·6; H, 4·1; S, 23·8%).

p-*Tolyl 2-Amino-4-methyl-5-thiazyl Sulphone.*—*p*-Tolyl 2-acetamido-4-methyl-5-thiazyl sulphide (20·0 g.) in acetic acid (250 c.c.) was oxidised with a solution of potassium permanganate (25·0 g.) in water (250 c.c.) added during 1 hour, sulphur dioxide was passed, and the solid collected and crystallised from alcohol giving colourless plates (12·0 g.), m. p. 238° (Found : C, 49·9, H, 4·3. $C_{12}H_{14}O_2N_2S_2$ requires C, 50·3; H, 4·5%). This *acetamido*-compound (10·1 g.) was hydrolysed by acid to the *amino-sulphone* which crystallised from benzene–light petroleum (b. p. 60—80°) in colourless needles (6·8 g.), m. p. 176° (Found : C, 49·0; H, 4·5. $C_{11}H_{12}O_2N_2S_2$ requires C, 49·1; H, 4·5%).

p-*Chlorophenyl 2-Amino-4-methyl-5-thiazyl Sulphone.*—The acetamido-sulphide was oxidised in the usual way with potassium permanganate; the p-*chlorophenyl 2-acetamido-4-methyl-5-thiazyl sulphone* crystallised from alcohol in colourless needles (53·3%), m. p. 266° (Found : C, 43·45; H, 3·55; S, 19·7. $C_{12}H_{11}O_3N_3ClS_2$ requires C, 43·6; H, 3·3; S, 19·4%). Hydrolysis with acid gave the *amino-sulphone*, which crystallised from benzene–light petroleum (b. p. 60—80°) in colourless prisms, m. p. 160° (Found : Cl, 12·5; S, 22·0. $C_{10}H_9O_2N_3ClS_2$ requires Cl, 12·3; S, 22·2%).

3-*Bromo*-1-p-*nitrobenzenesulphonylacetone.*—*p*-Nitrobenzenesulphonylacetone (27·0 g.) in acetic acid (250 c.c.) at 40° was treated with bromine (18·0 g.) in acetic acid (100 c.c.) and shaken until the colour was (suddenly) discharged. The pale yellow solution was poured into water (1 l.), the solid collected, and crystallised from dilute acetic acid giving large colourless needles (32·5 g.), m. p. 149° (Found : Br, 25·0; S, 9·8. $C_9H_8O_5NBrS$ requires Br, 24·9; S, 9·9%). When this *compound* (3·2 g.) in alcohol (100 c.c.) was refluxed with sodium *p*-nitrothiophenoxide (1·8 g.) for 1 hour and the solution poured into water a solid *sulphide-sulphone* was obtained which crystallised from β-ethoxyethanol in yellow prisms (1·5 g.), m. p. 168° (Found : C, 45·35; H, 3·2; S, 16·3. $C_{15}H_{13}O_7N_3S_3$ requires C, 45·45; H, 3·0; S, 16·2%). On oxidation of this compound (1·0 g.) in boiling acetic acid (10 c.c.) by hydrogen peroxide (100-vol., 1·2 c.c.) a disulphone was precipitated on pouring into water; it crystallised from β-ethoxyethanol giving large golden yellow prisms (0·6 g.), m. p. 188—189°, identical with 1 : 3-*bis*-p-*nitrobenzenesulphonylacetone* prepared as below (Found : C, 42·4; H, 2·75; S, 15·0. $C_{15}H_{12}O_9N_2S_2$ requires C, 42·05; H, 2·8; S, 14·9%).

1 : 3-*Bis*-p-*nitrobenzenesulphonylacetone.*—*s*-Dichloroacetone (12·7 g.) and sodium *p*-nitrothiophenoxide (35·0 g.) were refluxed in alcohol (500 c.c.) for 6 hours, poured into water, and the *disulphide* collected, washed with water and crystallised from β-ethoxyethanol giving golden yellow plates (12·8 g.), m. p. 156° (Found : C, 49·2; H, 3·1; S, 17·3. $C_{15}H_{12}O_6N_2S_2$ requires C, 49·45; H, 3·3; S, 17·6%). When this disulphide (3·6 g.) in boiling acetic acid (30 c.c.) was oxidised with hydrogen peroxide (100-vol., 9 c.c.) the disulphone was precipitated on pouring into water and crystallised from β-ethoxyethanol giving large golden yellow prisms (2·9 g.), m. p. 188—189° (Found : C, 42·2; H, 2·5; S, 15·4. Calc. for $C_{15}H_{12}O_9N_2S_2$: C, 42·05; H, 2·8; S, 14·9%).

2-*Amino*-4-(p-*nitrophenylsulphonylmethyl*)*thiazole.*—3-Bromo-1-*p*-nitrobenzenesulphonylacetone (32·0 g.) and thiourea (7·6 g.) were refluxed in alcohol (200 c.c.) for 2 hours, water (500 c.c.) added, the solution filtered (charcoal), the filtrate made just alkaline with ammonia, and the precipitate collected and crystallised from β-ethoxyethanol giving almost colourless prisms of the *compound* (23·0 g.), m. p. 238° (Found : C, 40·35; H, 3·1; S, 21·4. $C_{10}H_9O_4N_3S_2$ requires C, 40·1; H, 3·0; S, 21·4%). The *acetyl* derivative, prepared with acetic anhydride, crystallised from β-ethoxyethanol giving colourless prisms, m. p. 204° (Found : C, 42·5; H, 3·5; S, 18·4. $C_{12}H_{11}O_5N_3S_2$ requires C, 42·2; H, 3·2; S, 18·8%). The above nitro-sulphones were reduced in alcohol with Raney nickel catalyst.

2-*Amino*-4-(p-*aminophenylsulphonylmethyl*)*thiazole* formed long slender faintly buff-coloured needles from β-ethoxyethanol, m. p. 229° (Found : C, 44·3; H, 4·1; S, 24·0. $C_{10}H_{11}O_2N_3S_2$ requires C, 44·6; H, 4·1; S, 23·8%).

1 : 3-*Disulphanilylacetone* formed colourless plates from alcohol, m. p. 187—188° (Found : C, 49·0; H, 4·5. $C_{15}H_{16}O_6N_2S_2$ requires C, 48·9; H, 4·3%).

Reaction of 2-p-*Nitrobenzenesulphenamido-4-methylthiazole with Acid in the Presence of Resorcinol.*—The sulphenamide (2·7 g.) was added to a refluxing solution of resorcinol (2·2 g. = 2 mols.) in alcohol (50 c.c.) and concentrated hydrochloric acid (5 c.c.) during 10 minutes, and the solvents were evaporated under reduced pressure and the residue treated with water (50 c.c.) and concentrated hydrochloric acid (1 c.c.). The insoluble residue was dissolved in dilute sodium carbonate solution, filtered (charcoal), precipitated with acid, and crystallised from acetic acid giving 4-nitro-2′ : 4′-dihydroxydiphenyl sulphide (0·25 g., m. p. 184°). The acid filtrate was made alkaline with sodium carbonate, and the solid collected and crystallised from benzene–light petroleum (b. p. 60—80°) giving a mixture of the two dimorphs of *p*-nitrophenyl 2-amino-4-methyl-5-thiazyl sulphide (1·9 g., m. p. 173°).

p-*Nitrophenyl 2-Amino-4-phenyl-5-thiazyl Sulphide.*—(A) 2-Amino-4-phenylthiazole (17·0 g.) was dissolved in hot benzene, cooled to 30°, and treated with a solution of *p*-nitrobenzenesulphenyl chloride (9·5 g.) in benzene (50 c.c.), water (300 c.c.) added, the solid collected, washed with hot water and crystallised from xylene giving golden-yellow plates (16·8 g.), m. p. 228° (Found : 54·85; H, 3·1; S,

19·4. $C_{15}H_{11}O_2N_3S_2$ requires C, 54·7; H, 3·3; S, 19·5%). This *compound* was recovered unchanged after boiling for 3 hours with concentrated hydrochloric acid and β-ethoxyethanol. With acetic anhydride (30 c.c.) at 100° the compound (5·0 g.) gave an *acetyl* derivative which crystallised from alcohol in colourless felted needles (3·8 g.), m. p. 208° (Found: C, 55·2; H, 2·4; S, 17·2. $C_{17}H_{13}O_3N_3S_2$ requires C, 55·0; H, 3·5; S, 17·3%), and was reconverted into the amino-sulphide, m. p. 228° (Found: S, 19·2%) by hydrolysis with concentrated hydrochloric acid and β-ethoxyethanol.

(B) 2-Amino-4-phenyl-thiazole (8·8 g.) was dissolved in hot chloroform (200 c.c.), cooled to 25°, and treated with bromine (8·0 g.) in chloroform (20 c.c.). After ½ hour the solvent was removed under reduced pressure, the residue dissolved in chloroform (100 c.c.), shaken with sodium carbonate solution, again evaporated under reduced pressure and the residue dissolved in hot *cyclo*hexane. On standing, *5-bromo-2-amino-4-phenylthiazole* separated in clumps of colourless needles (8·1 g.), m. p. 106° (Found: C, 43·1; H, 2·6; Br, 31·4; S, 12·7. $C_9H_7N_2BrS$ requires C, 42·4; H, 2·7; Br, 31·4; S, 12·5%).

The bromo-compound (2·6 g.) and sodium *p*-nitrothiophenoxide (1·9 g.) were refluxed in alcohol (50 c.c.) until the colour was discharged (½ hour), poured into water, and the solid collected and crystallised from xylene giving yellow plates (1·2 g.), m. p. 228° not depressed by *p*-nitrophenyl 2-amino-4-phenyl-5-thiazyl sulphide prepared by method (A) (Found: C, 54·5; H, 3·1; S, 19·7%).

p-*Nitrophenyl 2-Amino-4-phenyl-5-thiazyl Sulphone.*—The above acetamido-sulphide (3·7 g.) was stirred in acetic acid (120 c.c.) at 85°, hydrogen peroxide (100-vol., 5 c.c.) added during ½ hour, the solution boiled for 1 hour, poured into water (500 c.c.), and the p-*nitrophenyl 2-acetamido-4-phenyl-5-thiazyl sulphone* collected and crystallised from β-ethoxyethanol giving pale yellow needles (2·3 g.), m. p. 253—255° (Found: C, 50·7; H, 3·25; S, 15·9. $C_{17}H_{13}O_5N_3S_2$ requires C, 50·6; H, 3·2; S, 15·9%). This acetamido-sulphone (2·0 g.) was hydrolysed by concentrated hydrochloric acid and β-ethoxyethanol to the *amino-sulphone* which crystallised from alcohol in slender yellow needles (1·1 g.), m. p. 238° (Found: C, 49·8; H, 3·05; S, 17·6. $C_{15}H_{11}O_4N_3S_2$ requires C, 49·9; H, 3·0; S, 17·7%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED, RESEARCH LABORATORIES,
BLACKLEY, MANCHESTER, 9.

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30. *The Place of Yttrium and the Application of Ferricyanide Precipitation in the Rare-earth Group. The Purification of Erbium.*

By JOSEPH K. MARSH.

Whereas it is believed that ionic and atomic radii sequences of the rare-earth elements (atomic numbers 57—71 inclusive) both follow the atomic number sequence, yttrium interpolates between holmium and dysprosium in ionic radius, and between neodymium and samarium in atomic radius. Examples of yttrium occupying the latter position are collected. Yttrium may be collected first in one and then in a second position in the rare-earth series, and so be readily eliminated and purified. Ferricyanide precipitation is reported upon favourably for the separation of yttrium from holmium and erbium. The reduction of yttrium in erbium from 7 to 0·32 atoms % was accomplished by six precipitations with 50% yield. A sample of 20 atomic % holmium oxide rose to 36% in the first two-fifths to be precipitated, and fell to 6·5% in the tail two-fifths when divided into four fractions.

THE ionic radius of yttrium from measurements of the oxide lattice size appears to fall between that of dysprosium and holmium, but other observations, *e.g.*, fractional crystallisations o bromates or dimethylphosphates, or measurement of molecular volume of hydrated sulphates (Hevesy, *Z. anorg. chem.*, 1925, **147**, 217; **150**, 68) place yttrium between holmium and erbium. Now, while the series of elements Nos. 57—71 on passing between ionic and covalent linkage may be expected to have a similarly graded series of properties so as to retain their relative stations, yttrium (No. 39) cannot be expected to maintain its ionic position between Nos. 67 and 68 when in a covalent state. The electron density of yttrium is lower, and it may be that the three additional electrons will produce a proportionately greater increase in radius. Indeed, Klemm and Bommer (*ibid.*, 1937, **231**, 138; 1939, **241**, 264) have measured the atomic volumes and derived atomic radii of the rare-earth metals, and it can be seen that this is so. Abnormally large radii were found for the three elements having distinct bivalent properties, and rather small volumes for cerium, praseodymium, and terbium. The others lay on a smooth curve when plotted against atomic number, and showed a fall from lanthanum (1·871 A.) to lutecium (1·737 A.), with yttrium (1·814 A.) taking a place just below neodymium (1·818 A.). Thus yttrium here rises five or six places in size order as compared with the yttrium ion in the ionic radius sequence. This suggests that separation of yttrium from the yttrium earths should be accomplished by using processes involving covalent linkages in place of ionic. Then we may expect it to accumulate between neodymium and samarium.

The Group VIII complex cyanides are worth studying in this connexion. A number of solubilities of ferro-, ferri-, and cobalti-cyanides have been determined. These are presented on p. 119 recalculated as milligram-atoms of rare earth per litre.

Solubility of rare-earth complex cyanides, in mg.-atoms/l.

E = Y.	La.	Ce.	Pr.	Nd.	Y.	Sm.	Gd.	Dy.	Er.	Yb.	Y/Er.
(*a*) —	32·6	—	14·2	9·13	5·33	1·54	0·75	1·60	0·74	—	7·2
(*b*) —	24·0	24·7	—	9·54	7·23	—	4·10	—	(1·9)	0·81	3·8
(*c*) —	45·2	19·7	18·8	5·3	4·3	1·6	—	—	—	2·6	—
(*d*) —	58·0	11·8	8·25	20·6	7·9	4·7	—	—	—	4·4	—
(*e*) 30·9	15·7	—	—	10·6	—	13·9	15·5	19·4	15·8	—	2·0
(*f*) 7·45	4·2	—	—	4·1	—	3·9	3·3	3·35	2·8	—	2·7
(*g*) 58·3	22·4	—	—	9·8	—	14·5	12·6	19·0	19·2	—	3·0

(*a*) Ferricyanides, $EFe(CN)_6.nH_2O$ ($n = 4$, except La and Dy, 4·5; Pr, 3) at 20° (Prandtl and Mohr, *Z. anorg. Chem.*, 1938, **236**, 243; **237**, 160).
(*b*) Cobalticyanides, $ECo(CN)_6.4{\cdot}5H_2O$ at 20° (James and Willand, *J. Amer. Chem. Soc.*, 1916, **38**, 1497).
(*c*) Cobalticyanides, found to be anhydrous (Karantaissis, Vassiliadis, and Perakis, *Compt. rend.*, 1939, **298**, 1720).
(*d*) As (*c*), but in 0·1N-hydrochloric acid.
(*e*) Ferrocyanide, $NaEFe(CN)_6.nH_2O$ ($n = 5$, 6, 7, 8, or 10) in 0·1N-HCl (Prandtl and Mohr, *loc. cit.*).
(*f*) Ferrocyanide, $KEFe(CN)_6.nH_2O$ ($n = 4$, 5, or 8) in 0·1N-HCl (*idem, ibid.*).
(*g*) Basic ferrocyanide, $E(OH)[EFe(CN)_6]_2.nH_2O$ ($n = 14$, 15, or 18) (*idem, ibid.*).

The above data serve to show that the solubility of yttrium is much greater in all instances than its neighbours in an ionic radius sequence. Among the ferri- and cobalti-cyanides it appears to take again a position as in the atomic volume sequence of the metals.

The behaviour of yttrium as a base may also be considered. It is well known to act as a stronger base than its neighbours in an ionic radius sequence. The situation has been fully reviewed recently by Moeller and Kremers (*Chem. Rev.*, 1945, **37**, 97; *J. Physical Chem.*, 1944, **48**, 395) who conclude that " the anomalously high basicity of yttrium as obtained by measurements upon natural mixtures is undoubtedly a concentration effect ". They bring evidence to show that yttrium can take its rightful place in the ionic sequence in an evaluation of basicity if disturbing factors are eliminated. This is shown by the pH of 0·1M-solutions after 40% precipitation as hydroxide. Here the pH value for yttrium falls between the values for erbium and gadolinium. On the other hand, at incidence of hydroxide precipitation the value found for yttrium placed it between samarium and neodymium. Trombe (*Compt. rend.*, 1943, **216**, 888) finds that pure yttrium shows a remarkably large dilution factor in its basic strength as measured by pH at initiation of hydroxide precipitation by gaseous ammonia in nitrate solutions. In dilute (0·005M) solution it appears to be almost as strong a base as lanthanum, but in concentrated (0·5M) solution it is weaker than dysprosium at the same concentration. Thus we may deduce that the high concentration of yttrium in natural mixtures should mask the potentially high basic strength of yttrium in dilute solution, and separation of pure yttrium by basic methods should fail whereas separation of a little yttrium from erbium should be easy. This is exactly the reverse of well-established practical experience. Some other factor of over-riding importance must be operative. Moeller and Kremers cite twelve orders of basicity of the rare earths arrived at by different experimental methods. In four cases (ammonia precipitation, and sulphate, nitrite, and azide hydrolysis) yttrium takes a place between neodymium and samarium, in three cases it lies somewhere between samarium and dysprosium, and in two (carbonate hydrolysis and electro-reduction) it lies next to holmium. Gaps in data leave the yttrium position in some doubt in the other three cases. The basic salts of yttrium are probably in general more stable than those of its neighbours in the ionic radius sequence. Moeller and Kremers find equilibrium pH to be established less quickly after each addition of alkali to yttrium solutions than with other rare-earth solutions. They ascribe this to the stability of a basic nitrate, and account similarly for the strong apparent basicity of yttrium which they regard as in reality spurious, but which is indicated by the high pH value for the incidence of precipitation of hydroxide from nitrate and sulphate solutions, as well as by much practical experience. The higher values for the pH at incidence of hydroxide precipitation from acetate solutions for all the rare earths as compared with nitrate and sulphate they ascribe to co-ordination, but obviously the same reasoning would apply to the high values for yttrium in nitrate and sulphate solutions. A co-ordinating tendency may masquerade as a strengthening of basic character.

The instances here mentioned [atomic volume, solubility of ferricyanide, pH at incidence of precipitation of hydroxide from nitrate or sulphate solution by ammonia, or from chloride solution by sodium hydroxide (Britton, *J.*, 1925, **127**, 2142), four fractionation methods by basic processes] in which yttrium takes a position in the series of rare earths between neodymium and samarium are too numerous to be fortuitous. In yet other instances, yttrium may occupy a

position between samarium and its place (close to holmium) where it is found in the pure ionic state. The former position appears to be connected with co-ordination or a covalent reaction and demonstrates that yttrium is not in all respects a typical yttrium group element. It may show a resemblance to scandium not seen in the earths of high atomic weight and comparable basicity. There is a qualitative difference between the yttrium ion and the holmium ion not taken into account by quantitative measurements of their respective basicities, but due to the differing inner constitutions of nucleus and electons.

Some reactions which can be formulated as ionic, for instance that between potassium ferricyanide and yttrium chloride, do not appear to be in fact ionic. It is possible to bring these substances together at high concentrations without any precipitate forming, and reaction only takes place slowly on gentle warming. Although yttrium in the product shows a normal ionic radius, the reaction separates yttrium from the yttrium earths in a manner to be expected in a non-ionic reaction.

The Purification of Erbium and Holmium.—The complex potassium ferrocyanide of yttrium and erbium was used by Prandtl (*Z. anorg. Chem.*, 1931, **198**, 157) for the purification of erbium, but his preparation was found later to be much less pure than he had supposed (Hönigschmid and Wittner, *ibid.*, 1937, **232**, 112). Moeller and Kremers (*J. Amer. Chem. Soc.*, 1944, **66**, 307) have further studied the purification of erbium by means of ferrocyanide. According to the data tabulated above, potassium yttrium ferrocyanide is 2·7 times as soluble as potassium erbium ferrocyanide. Ferricyanides on the other hand will be seen to show a 7-fold greater solubility for yttrium than for erbium. Prandtl and Mohr (*loc. cit.*) have recommended the use of ferricyanides for the preliminary elimination of yttrium from the yttrium earths before proceeding with their separation, but give few details of the method. The author has found it useful not only for the preliminary separation of yttrium but also for the ultimate purification of erbium and for the concentration of holmium following a bromate fractionation. He has previously recommended the use of dimethylphosphates (*J.*, 1939, 554) for separation of holmium and yttrium, and this salt probably remains the most useful for the final stage, but after a bromate fractionation has separated erbium and holmium the use of ferricyanide precipitation will again be useful to eliminate the bulk of the yttrium to yield a 80—90% holmium preparation for dimethylphosphate treatment. Since dimethylphosphates tend to hydrolyse, especially the less soluble ones, and since the sparingly soluble hydrolysis products tend to collect at the head, the dimethylphosphate fractionation of erbium will not be expected to eliminate yttrium satisfactorily. Any slight loss of holmium through hydrolysis will collect with yttrium at the head and leave pure holmium lower down the series, but the purification of erbium must be completed by the ferricyanide process. The six best holmium oxide fractions from the author's previously reported holmium fractionation have now been quantitatively analysed for yttrium by the cathode layer method and found to average about 0·03% of yttrium oxide by weight.

A loss of 1—2% was common in each ferricyanide precipitation and hydrolysis. Considering the comparatively few operations required, these losses are not intolerable. The technique of the process is simpler than for the ferrocyanides and the separation more rapid. Six precipitations of 93% erbium gave a 50% yield of 99·7 atomic % material, or by weight 96% oxide became 99·80 $\pm$ 0·05%.

Experimental.

The Reaction between Rare-earth Chloride and Potassium Ferricyanide.—The precipitation of rare-earth ferricyanide is possible from chloride solution at any temperature between 15° and 100° by addition of concentrated potassium ferricyanide solution, but at low temperatures high concentrations of rare earth, of the order of 200 g./l. of oxide, must be used. Initiation of the reaction is not always smooth, but slow precipitation gives the best fractional separations. Thus it was sometimes advantageous to warm a small portion of the chloride–ferricyanide solution separately till a heavy precipitate was formed and to add this to the main bulk. The main warming was done not more rapidly than 1°/5 mins. at temperatures where precipitation was expected to begin. It was also advantageous to lower the temperature with cold water or ice by 10—15° once the precipitation was well established. Mechanical stirring was applied while the ferricyanide solution was added dropwise. Precipitates formed in boiling solution are bright blood-red, crystalline, and settle immediately; those from cold solutions clay-like and more brick-red. Precipitation temperatures of 40—60° appeared most favourable, with precipitation starting by the time one-third of the potassium ferricyanide to be used had been added. The addition took 1—2 hours but the precipitate became more crystalline when the reaction mixture was kept warm and stirred for a further 3 hours. Precipitation was tried from a boiling chloride solution containing 10 g./l. of oxide but the separation was less effective than from warm solutions of 50—100 g./l. of oxide. Small amounts of free hydrochloric acid, or the accumulation of potassium chloride in the mother-liquors, caused no difficulty. The presence of a small amount of iron was also immaterial.

The ferricyanide precipitates were treated with an equivalent of cold 5N-alkali, whereby ready hydrolysis took place and potassium ferricyanide could be recovered. The filter cake of hydroxides

required treating two or three times again with more dilute cold alkali till the filtrate showed little colour. There was an equilibrium between hydroxide and ferricyanide which made quantitative removal of iron impracticable. The almost iron-free filter cake was dissolved in hydrochloric acid to yield a blue solution. The Prussian-blue, if desired, was destroyed by boiling with a little potassium chlorate. The solution was neutralised, and provided the rare-earth oxide did not amount to more than 100 g./l., ferric hydroxide was precipitated satisfactorily and was removed before proceeding to the next ferricyanide precipitation.

Ferricyanide Precipitation of a Crude Yttrium Earth.—The following table shows the apparent atomic weights and proportions of a crude yttrium earth from gadolinite, following a double sulphate treatment, when submitted to fractional precipitation as ferricyanide. The final fraction (6) was the unprecipitated portion remaining in the mother-liquor and recovered as hydroxide.

	(*a*) 250 G./l.; boiling.		(*b*) 100 G./l.; boiling.		(*c*) 40 G./l.; boiling.		(*d*) 75 G./l.; 40–60°	
	At. wt.	%.	At. wt.	%.	At. wt.	%.	At. wt.	%.
1	115	11	116	9	118	12	120	13
2	111	16	118 *	18	112	22	112	16
3	108	15	109	20	107	19	107	16
4	102	22	99	24	101	22	101	13
5	96	22	94	20	91	21	98	12
6	90	14	90	9	90	4	92	30

* Reaction interrupted.

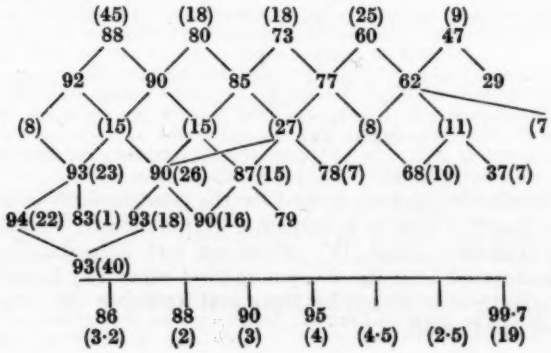
The reactions at 100° were each completed in about 20 mins. in solutions stirred by a steam jet with the ferricyanide solution (1 g. in 3 ml.) added dropwise in 15 mins. Each precipitate in (*d*) was produced by adding potassium ferricyanide amounting to one-third of the original weight of rare earth. After the second precipitation the solution was concentrated to its original concentration. Precipitates 1—4 were obtained at 40—50°, but 5 required heating to 60° as the solution again became dilute. This series, rather more successful than those at 100°, took longer to perform but not more attention.

The holmium absorption band λ 5360 was compared in fractions (*d*, 1) and (*d*, 6) by bringing it to the same small intensity in each as matched by eye with a direct vision spectroscope. It was concluded that it was 8 times stronger in (*d*, 1). The erbium bands in the green region could not be compared, for a trace of neodymium interfered. About 0·1% of neodymium was found in (*d*, 1) and 0·6% in (*d*, 6) by comparison of light absorption in the orange region. The colour of the oxides decreased from head to tail, showing that terbium was collecting at the head. The head fraction is estimated to have contained about 40% of non-yttrium oxides, and the tail 4—5%. The first 45% contained 75% and the last 30% about 6·4% of the original non-yttrium oxides.

Separation of Yttrium and Erbium.—The starting material had been fractionated as bromate and by nitrate fusions. It was converted into neutral chloride, and the solution fractionally precipitated with potassium ferricyanide (1 g. in 3 ml.) from solutions originally containing the equivalent of about 100 g./l. of oxide. The fractionation was controlled by determinations of the apparent atomic weight from oxide–oxalate ratios in separate portions of oxalate, about 50 mg. of oxalate and 0·02N-potassium permanganate being used for each oxalate titration. The following is a typical result :

	Input.	Output.					
Fraction.		1.	2.	3.	4.	5.	6.
Atomic weight	120	141	134	128	123	113	97
% of total erbium atoms	—	29	21	17	12	14	7
Erbium atoms, % of metal	40	67	59	51	44	31	10
% of output	102	17	14	13	11	18	26
Erbium oxide, % by wt. (approx.) ...	52	80	75	67	60	45	17
Erbium oxide, % by wt. } M. and K.	57	89	86	80	62	38	Low
% of output }	104	12	5	14	17	16	36

Comparison is shown with a ferrocyanide fractionation reported by Moeller and Kremers (*loc. cit.*) after 28 fractional precipitations (five series on five or six fractions). The results of 27 precipitations on some rich earths are shown diagramatically. The figures in parentheses show the weights (in g.), and the others show the % of erbium atoms.



For the final purification of erbium the rich material (93%) was precipitated with excess of ferricyanide from solutions containing initially 25—40 g./l. of oxide, at 40—50° with stirring for 5—6 hours. The mother-liquors then contained about 2 g./l. of unprecipitated oxides. Six such precipitations decreased the earth by 50% but reduced the yttrium to 0·32 ± 0·07 atomic %.

Fractionation of Holmium.—A sample of yttrium–holmium oxide, about 20 molecular % Ho_2O_3, was made into chloride solution equivalent to 20 g./l. of oxide and precipitated at 55° with potassium ferricyanide (1 g. in 3 ml.) equal to half the weight of oxide. The solution was then concentrated to 30 g./l., and two more precipitations made at 40—50° with further portions of ferricyanide. The yields were: (1) 18% of input with 39% Ho; (2) 20% with 33% Ho; (3) 18% with 17·5% Ho; (4) 40% with 6·5% Ho (not precipitated). There are thus over five times as many holmium atoms in the first 40% to be precipitated as in the last 40%.

The estimates of yttrium in the purified holmium and erbium oxides were made by diluting the oxides with 4 and 9 times their weights of alumina respectively and arcing and spectrographing the cathode layer. The resulting spectrograms were compared with standards prepared from pure yttria in alumina. The possible effect of the holmia and erbia on the intensities of the yttrium arc lines could not be estimated but was not considered likely to exceed 20% in the case of erbium.

This spectroscopic work was carried out by Dr. R. O. Scott of the Macaulay Institute for Soil Research, Aberdeen, to whom the author tenders thanks. The author also thanks Dr. A. S. Russell for permission to use this laboratory.

DR. LEE'S LABORATORY, CHRIST CHURCH, OXFORD. [*Received, May 24th*, 1946.]

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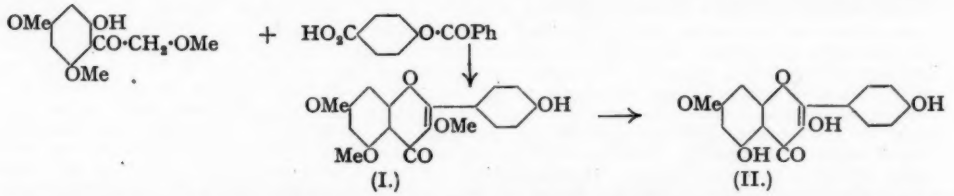
31. *Synthesis of the Monomethyl Ethers of Kaempferol, and the Constitution of Rhamnocitrin.*

By K. VISWESWARA RAO and T. R. SESHADRI.

The 3- and 7-monomethyl ethers of kaempferol (3 : 5 : 7 : 4′-tetrahydroxyflavone) have been newly synthesised and the 4′-methyl ether (kaempferide) prepared by a procedure different from that of Heap and Robinson. The 7-methyl ether is identical with rhamnocitrin. The 3-methyl ether is named "*iso*kaempferide".

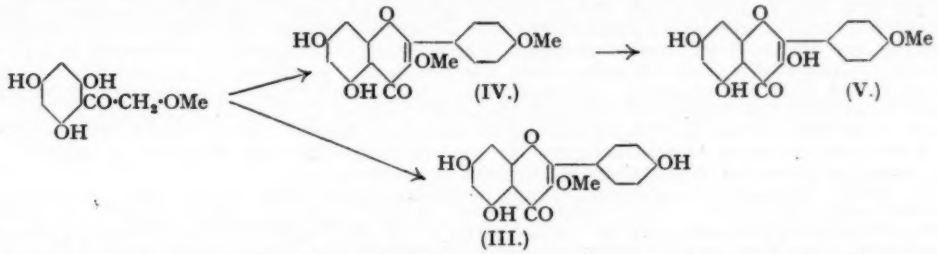
THE constitution of kaempferide, a component of galanga root, was confirmed as kaempferol 4′-methyl ether by synthesis (Heap and Robinson, *J.*, 1926, 2336). Tschirch and Polacco (*Arch. Pharm.*, 1900, **238**, 459) gave the name rhamnocitrin to one of the compounds isolated from the berries of *Rhamnus catharticus*; later, Oesch and Perkin (*J.*, 1914, **105**, 2350) determined its composition and showed that it was another monomethyl ether of kaempferol, although it bore considerable resemblance to kaempferide: it crystallised in yellow leaflets, m. p. 221—222°, and its acetyl derivative had m. p. 200—201°, whereas kaempferide crystallised as yellow needles, m. p. 227—229°, and its acetate melted at 193—194°. Oesch and Perkin, however, suggested that further work on this subject was desirable, and we now give synthetic evidence on the matter. We have prepared the 3- and the 7-methyl ether of kaempferol, and for comparison, we have made the 4′-methyl ether by partial demethylation of the 3 : 4′-dimethyl ether.

For the synthesis of the 7-methyl ether (II), 2-hydroxy-ω : 4 : 6-trimethoxyacetophenone was condensed with the potassium salt and anhydride of *p*-benzoyloxybenzoic acid according to the method of Allan and Robinson, and the resulting 4′-*hydroxy*-3 : 5 : 7-*trimethoxyflavone* (I) afforded (II) on partial demethylation with aluminium chloride in nitrobenzene solution.



When ω-methoxyphloroacetophenone is used for the condensation with the same anhydride and potassium salt, the 3-*methyl ether* of kaempferol (III) is directly obtained. By using anisic acid instead, the 3 : 4′-dimethyl ether (IV) (Robinson and Shinoda, *J.*, 1925, **127**, 1973) is produced and this is converted into the 4′-monomethyl ether (V) by partial demethylation. This compound was originally synthesised by Heap and Robinson (*loc. cit.*) from ω-benzoyloxyphloroacetophenone and anisic acid.

Of the three monomethyl ethers, (II) agrees entirely with rhamnocitrin in all its properties. This formulation for rhamnocitrin is also in accordance with expectation, since it occurs in the



berries of *Rhamnus catharticus* along with rhamnetin, the 7-methyl ether of quercetin, the free flavonols kaempferol and quercetin being the other components (Oesch and Perkin, *loc. cit.*). The 5-monomethyl ether would not be expected to occur in Nature since this position is difficult to methylate, and hence it has not been taken into consideration here. Though the 3-methyl ether (III) has not so far been identified among natural products, it may occur just like the 3-methyl ether of galangin present in the galanga root. It is therefore assigned the name of "*iso*kaempferide".

Experimental.

p-*Benzoyloxybenzoic Acid.*—By Schotten–Baumann benzoylation of *p*-hydroxybenzoic acid (10 g.) with benzoyl chloride (10 c.c.), 15 g. of the benzoyl acid were obtained. It crystallised from alcohol as colourless needles, m. p. 221—223° (Found: C, 69·5; H, 4·3. Calc. for $C_{14}H_{10}O_4$: C, 69·4; H, 4·1%).

Anhydride. The acid (10 g.) was suspended in dry carbon tetrachloride (25 c.c.) and treated with portions of phosphorus pentachloride while being heated on a water-bath till a clear solution resulted. The solvent and phosphorus oxychloride were distilled off under reduced pressure and the crude acid chloride (8·5 g.) was taken up in anhydrous ether (400 c.c.). Dry pyridine (50 c.c.) was added to the ethereal solution, which was kept at 0° for 3 hours; small pieces of ice and ice-cold dilute hydrochloric acid were then added, with stirring. The solid *product* was filtered off, macerated successively with cold dilute hydrochloric acid, aqueous sodium carbonate, and cold water, and dried in the vacuum desiccator; it (7 g.) crystallised from dry benzene in rectangular prisms, m. p. 155—157° (Found: C, 72·5; H, 4·2. $C_{28}H_{18}O_7$ requires C, 72·1; H, 3·9%).

Potassium salt. This was prepared by adding alcoholic potash dropwise to a solution of the dry acid in absolute alcohol–ether, using phenolphthalein as indicator. The precipitated potassium salt was filtered off, washed with ether, and dried in a vacuum desiccator.

4′-*Hydroxy*-3 : 5 : 7-*trimethoxyflavone* (I).—An intimate mixture of 2-hydroxy-ω : 4 : 6-trimethoxyacetophenone (1 g.), *p*-benzoyloxybenzoic anhydride (5 g.) and potassium *p*-benzoyloxybenzoate (2 g.) was heated in a vacuum at 180—185° for 3 hours. The resulting solid cake was powdered and refluxed with 10% alcoholic potash (50 c.c.) for 20 minutes, giving a clear solution. The solvent was then distilled off under reduced pressure, and the product dissolved in water (150 c.c.). The clear brown solution was saturated with carbon dioxide and a yellow solid separated in good yield. It was filtered off and washed with water; yield, 1 g. This *flavone* was very sparingly soluble in benzene, ethyl acetate, or alcohol and moderately soluble in glacial acetic acid, from which it crystallised in pale yellow, rhombic plates and prisms, m. p. 278—280° (Found: C, 65·9; H, 5·0. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%). It was readily soluble in aqueous sodium hydroxide to give a yellow solution and did not give any characteristic coloration with ferric chloride. In concentrated sulphuric acid it exhibited a greenish-blue fluorescence.

On acetylation by means of acetic anhydride and a few drops of pyridine it yielded the *acetate*, which crystallised from methyl alcohol as colourless needles, m. p. 147—149° (Found: C, 64·7; H, 4·5. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%). On methylation by methyl sulphate and anhydrous potassium carbonate in dry acetone, (I) yielded the methyl ether, which was insoluble in aqueous sodium hydroxide. This crystallised from benzene–light petroleum in colourless, rectangular plates, m. p. 165—166°, not depressed in admixture with an authentic sample of kaempferol tetramethyl ether. The compound gave a bright greenish-blue fluorescence in concentrated sulphuric acid.

3 : 5 : 4′-*Trihydroxy*-7-*methoxyflavone* (*Rhamnocitrin*) (II).—The trimethyl ether (I) (0·5 g.), dissolved in dry nitrobenzene (15 c.c.), and aluminium chloride (1 g.) in the same solvent were heated at 100° for 1 hour, and the mixture cooled and treated with excess of light petroleum (100 c.c.). The precipitated yellowish-brown solid was filtered off under suction and washed free from nitrobenzene with light petroleum. The residual aluminium chloride complex was then decomposed by heating with dilute hydrochloric acid (100 c.c.) on a water-bath for ½ hour. The bright yellow solid was collected, washed with water, and crystallised successively from ethyl acetate–light petroleum and methyl alcohol, separating from the latter as yellow leaflets, m. p. 220—222° (Found: C, 63·8; H, 4·2; OMe, 10·2. Calc. for $C_{16}H_{12}O_6$: C, 64·0; H, 4·0; OMe, 9·7%). This product was easily soluble in alcohol and ethyl acetate and sparingly in toluene. In aqueous sodium hydroxide it formed a yellow solution. With alcoholic ferric chloride an olive-green colour was produced, and with lead acetate an orange-yellow precipitate was formed. In concentrated sulphuric acid it exhibited a brilliant peacock-blue fluorescence.

The acetate (acetic anhydride and pyridine) crystallised from absolute alcohol–light petroleum in colourless, rectangular plates, m. p. 200—201°.

5 : 7 : 4′-*Trihydroxy*-3-*methoxyflavone* (iso*Kaempferide*) (III).—An intimate mixture of ω-methoxyphloroacetophenone (1 g.) and the anhydride (10 g.) and potassium salt (3 g.) of *p*-benzoyloxybenzoic acid was heated at 180—185° for 3 hours. The solid product was finely powdered, and hydrolysed by refluxing with 10% alcoholic potash (150 c.c.) for 20 minutes, whereby a clear solution resulted. After removal of solvent under reduced pressure, the residue was dissolved in water (200 c.c.), and the clear brown solution saturated with carbon dioxide. A dark brown solid separated and this as well as the solution was repeatedly extracted with ether. On distillation of solvent from the extract a light cream-coloured solid was obtained. iso*Kaempferide* was purified by crystallising twice from ethyl alcohol, forming tiny, rectangular plates, m. p. 270—272° (Found: C, 64·3; H, 4·4. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%). It was easily soluble in aqueous sodium hydroxide to give a bright yellow solution, and gave a brown colour with ferric chloride; no precipitate was formed with lead acetate. In concentrated sulphuric acid it produced a feeble blue fluorescence.

The *acetate*, prepared in the usual manner, crystallised from ethyl acetate–light petroleum in colourless needles, m. p. 161—163° (Found: C, 61·8; H, 4·2. $C_{22}H_{18}O_9$ requires C, 62·0; H, 4·2%).

3 : 5 : 7-*Trihydroxy*-4′-*methoxyflavone* (*Kaempferide*) (V).—5 : 7-Dihydroxy-3 : 4′-dimethoxyflavone (IV) (Robinson and Shinoda, *loc. cit.*) (0·5 g.) was partly demethylated exactly as in the preparation of rhamnocitrin (above), and the yellow solid finally obtained crystallised from methyl alcohol as golden-yellow needles, m. p. 227—229° (Found: C, 63·9; H, 4·0. Calc. for $C_{16}H_{12}O_6$: C, 64·0; H, 4·0%). It was soluble in aqueous sodium hydroxide to a yellow solution. It gave a greenish-brown colour with ferric chloride and a yellow precipitate with lead acetate in alcoholic solution. In concentrated sulphuric acid it gave a bright bluish-green fluorescence. The acetate, crystallised from methyl alcohol, formed colourless, narrow, rectangular plates, m. p. 191—193°.

ANDHRA UNIVERSITY, WALTAIR. [*Received, May 25th*, 1946.]

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32. *The Sulphonation of Some Derivatives of Eugenol.*

By G. R. CLEMO and J. H. TURNBULL.

The sulphonation of "dihydroeugenol" and of its acetyl and *O*-methyl derivatives is described. The sulphonic acids obtained have been orientated by synthesis of their methyl ethers from known aminomethyldihydroeugenols.

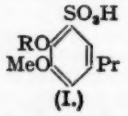
O-Methyleugenol and *O*-acetyleugenol have been shown to yield sultones on sulphonation. The mode of formation of these sultones is discussed and their structure has been established by synthesis.

THE sulphonation of "dihydroeugenol" (2-methoxy-4-*n*-propylphenol) has not hitherto been fully investigated, although there is a reference to the preparation of a single unorientated dihydroeugenolsulphonic acid (D.R.-P. 487,380; *Chem. Zentr.*, 1930, II, 985).

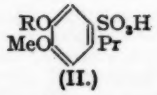
Further work on the sulphonation of dihydroeugenol is now described. Sulphonation at 0° yielded the 5-sulphonic acid (I, R = H) which was isolated as the barium salt and converted into the *p*-chlorobenzyl-ψ-thiouronium derivative (Dewey and Sperry, *J. Amer. Chem. Soc.*, 1939, **61**, 3251). The sulphonation of acetyldihydroeugenol with sulphuric acid at 0° gave similarly 5-hydroxy-4-methoxy-2-*n*-propylbenzenesulphonic acid (II, R = H).

The sulphonic acids (I and II; R = H) were methylated by boiling with methyl sulphate and aqueous potassium hydroxide giving their O-*methyl ethers* (I and II, R = Me). The latter (II, R = Me) was also obtained by sulphonation of *O*-methyleugenol.

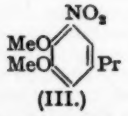
The methylated sulphonic acids were synthesised from 5- and 6-amino-*O*-methyldihydroeugenols, and the orientation of the acids (I and II, R = H) was thereby confirmed. 3-*Nitro*-4 : 5-*dimethoxy*-n-*propylbenzene* (III) was made by methylation of 5-nitrodihydroeugenol, and gave the corresponding *amino*-compound on reduction. Treatment of the diazotised amine by Gattermann's method (*Ber.*, 1899, **32**, 1140) yielded the sulphinic acid from which the sulphonic acid (I, R = Me) was obtained by oxidation. The isomer (II, R = Me) was prepared in a similar way from the appropriate amine. All the sulphonic acids were identified as their *p*-chlorobenzyl-ψ-thiouronium salts.



(I.)



(II.)



(III.)

The potassium dihydroeugenolsulphonates showed no antibacterial activity against a wide range of bacteria in inhibition tests.

Eugenol and its *O*-methyl and -acetyl derivatives show a marked difference from the corresponding dihydroeugenols in their behaviour towards sulphuric acid. Whereas the latter dissolve in the concentrated acid to give only faintly coloured solutions, the former compounds

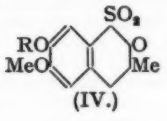
dissolve to give viscous intensely red solutions which evidently contain complex products. Hitherto no work appears to have been done on the nature of these.

Treatment of eugenol with concentrated sulphuric acid at 0° gave largely sulphonated polymers. When *O*-methyleugenol, however, was sulphonated by stirring with sulphuric acid at 0°, and the sulphonic acids were extracted with water, an amorphous mass was left from which a 5% yield of the *sultone* (IV, R = Me) was isolated. The aqueous extracts were neutralised with barium carbonate but attempts to separate the resulting amorphous mixture of barium sulphonates failed. It probably consisted largely of sulphonated polymers.

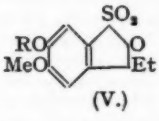
O-Acetyleugenol reacted with sulphuric acid in a similar way to methyleugenol, and the *sultone* (IV, R = H) was isolated from the sulphonation product. The substance gave a crystalline *acetate* on acetylation, and on methylation yielded the above sultone (IV, R = Me).

By analogy with the corresponding dihydroeugenols, *O*-methyl- and *O*-acetyl-eugenol would be expected to undergo nuclear sulphonation to give the *o*-allylsulphonic acid (VI), which might rearrange to give a δ- or γ-sultone (IV or V). A more probable explanation of sultone formation, however, is that the allylsulphonic acid undergoes addition of sulphuric acid at the double bond in accordance with Markownikow's rule (cf. the addition of hydrogen halides to eugenol; *J.*, 1945, 533) to give the sulphuric ester (VII) which on hydrolysis (cf. Brooks and Humphrey, *J. Amer. Chem. Soc.*, 1918, **40**, 822; Burgin, Hearne, and Rust, *Ind. Eng. Chem.*, 1941, **33**, 385) and lactonisation of the hydroxy-acid would then yield a δ-sultone (IV).

O-Methyleugenol reacted with 80% sulphuric acid at 5° to give β-3 : 4-*dimethoxyphenyliso-propyl alcohol*, and a small yield of the same product was obtained by treatment of *O*-methyleugenol with 85% phosphoric acid at 80°. This result lends support to the view that a sulphonated sulphuric ester acts as an intermediate in sultone formation. Eugenol was more susceptible to polymerisation than its *O*-methyl ether, and attempts to hydrate the double bond were unsuccessful.



(IV.)



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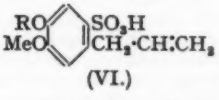

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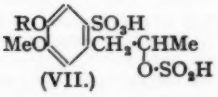

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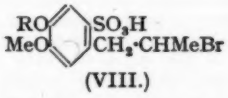
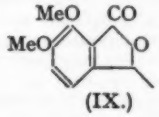


(VIII.)



(IX.)

γ-Sultones have been described by several workers (Sachs, Wolff, and Ludwig, *Ber.*, 1904, **37**, 3253; List and Stein, *ibid.*, 1898, **31**, 1648; Marckwald and Frahne, *ibid.*, p. 1854; Shearing and Smiles, *J.*, 1937, 1348), but δ-sultones are uncommon (cf. Nilsson, *Svensk Kem. Tidskr.*, 1940, **52**, 324). The δ-sultone structure (IV) is clearly indicated by the following synthesis: β-bromodihydroeugenol methyl ether (β-3 : 4-dimethoxyphenyl*iso*propyl bromide) (Merck, D.R.-P., 274,350; *Chem. Zentr.*, 1914, I, 2079) was sulphonated to give the unstable sulphonic acid (VIII, R = Me) which lost hydrogen bromide when its aqueous solution was boiled, giving the sultone (IV, R = Me). β-Bromodihydroeugenol (*J.*, 1945, 533) was converted into the acetate, which was sulphonated with loss of the acetyl group, yielding the bromosulphonic acid (VIII, R = H). An aqueous solution of this acid lactonised on boiling to give the sultone (IV, R = H).

The eugenol sultones, unlike the physiologically active lactones of the meconine type (IX; cf. Lautenschläger, *Chem. Zentr.*, 1921, III, 1366), were found to be devoid of anthelmintic activity. The toxicity of the sultones to mice was low, but they showed no activity against *Streptococci* or against trophozoite-induced *P. gallinaceum* infection in chicks.

Experimental.

2-Hydroxy-3-methoxy-5-n-propylbenzenesulphonic (*Dihydroeugenol-5-sulphonic*) *Acid* (I, R = H).—Dihydroeugenol (10 g.) was cooled to 0°, and concentrated sulphuric acid (6·4 c.c.) was dropped in during one hour with stirring. The product was kept for 24 hours at room temperature, ice added, and the solution extracted with ether, diluted, heated to boiling, and neutralised (Congo-red) with barium carbonate. The mixture was filtered and the filtrates concentrated, the barium salt crystallising in creamy-white needles (14 g.). The *benzyl-ψ-thiouronium* derivative, prepared in aqueous solution and crystallised from 50% alcohol, formed colourless leaflets, m. p. 109—112° (Found: C, 52·2; H, 5·5. $C_{10}H_{14}O_5S,C_8H_{10}N_2S$ requires C, 52·4; H, 5·8%). The *p-chlorobenzyl-ψ-thiouronium* derivative formed colourless plates, m. p. 168—170° (Found: N, 6·1. $C_{10}H_{14}O_5S,C_8H_9N_2ClS$ requires N, 6·3%).

The *potassium* sulphonate, prepared from an aqueous solution of the barium salt, crystallised from water in colourless prisms, and gave a deep blue coloration with ferric chloride (Found : K, 13·6. $C_{10}H_{13}O_5SK$ requires K, 13·7%). The pH of the salt in 0·1N-aqueous solution was 6·2—6·4 (capillator method).

5-Hydroxy-4-methoxy-2-n-propylbenzenesulphonic (*Dihydroeugenol-6-sulphonic*) *Acid* (II, R = H).—*O*-Acetyldihydroeugenol (10 g.) was dropped into concentrated sulphuric acid (20 c.c.) during 3·5 hours at 0—5° with stirring. The product was worked up as in the foregoing sulphonation to afford the barium salt, which crystallised from water (charcoal) in clusters of small, creamy-white needles (8 g.). The p-*chlorobenzyl-ψ-thiouronium* salt formed colourless prisms, m. p. 169—170°, after sintering at 156° (Found : C, 48·2; H, 5·4. $C_{10}H_{14}O_5S,C_8H_9N_2ClS$ requires C, 48·3; H, 5·2%). The *potassium* sulphonate, prepared from the barium salt, recrystallised from water in creamy-white prisms and gave a dull blue coloration with ferric chloride (Found : K, 13·8%). The pH of its 0·1N-aqueous solution was 6·2—6·4.

Sulphonation of O-*Methyldihydroeugenol.*—Concentrated sulphuric acid (1·1 g.) was dropped into the methyl ether (1 g.) with stirring. The mixture was warmed at 60° for 7 hours, and the barium 4 : 5-dimethoxy-2-*n*-propylbenzenesulphonate (cf. II, R = Me) isolated as in the previous sulphonations as a white crystalline solid (1·25 g.). The benzyl-*ψ*-thiouronium derivative formed colourless needles, m. p. 185—187°. The p-*chlorobenzyl-ψ-thiouronium* derivative formed clusters of white needles, m. p. 158° (sintering at 145—148°) (Found : C, 49·9; H, 5·2; N, 6·4. $C_{11}H_{15}O_5S,C_8H_9N_2ClS$ requires C, 49·4; H, 5·5; N, 6·1%). The *potassium* salt crystallised from water in slender white prisms (Found : K, 10·9. $C_{11}H_{15}O_5SK,3H_2O$ requires K, 11·1%).

3-Nitro-4 : 5-dimethoxy-n-propylbenzene (*5-Nitromethyldihydroeugenol*) (III).—5-Nitrodihydroeugenol (3·3 g.) (Levin and Lowy, *J. Amer. Chem. Soc.*, 1933, **55**, 1995), xylene (70 c.c.), and sodium bicarbonate (12 g.) were stirred under reflux with methyl sulphate (4 c.c.) for 5 hours. The xylene solution was washed with water and sodium hydroxide solution, the xylene removed, and the residue distilled, affording a pale yellow oil (3 g.), b. p. 145—150°/2 mm. (Found : C, 58·3; H, 6·5. $C_{11}H_{15}O_4N$ requires C, 58·7; H, 6·7%). This *nitro*-compound (6·4 g.) was dissolved in alcohol (10 c.c.) saturated with hydrogen chloride at 0° and mixed with a solution of stannous chloride (29·4 g.) in alcohol (50 c.c.) also saturated with hydrogen chloride. After 24 hours the alcohol was removed, and water and excess of sodium hydroxide solution added; the *3-amino*-compound, isolated by extraction with ether, distilled as a colourless oil (4 g.), b. p. 128—131°/2 mm. (Found : C, 67·0; H, 8·8. $C_{11}H_{17}O_2N$ requires C, 67·6; H, 8·8%). Its *hydrochloride* crystallised from acetone–methanol in clusters of white needles, m. p. 207° (Found : C, 56·4; H, 7·2. $C_{11}H_{17}O_2N,HCl$ requires C, 57·0; H, 7·7%). The *benzoyl* derivative crystallised from light petroleum (b. p. 40—60°) in long, silky needles, m. p. 67—69° (Found : C, 72·2; H, 7·3. $C_{18}H_{21}O_3N$ requires C, 72·4; H, 7·1%).

O-*Methyldihydroeugenol-5-sulphonic Acid* (I, R = Me).—The foregoing amino-compound (0·5 g.) was dissolved in concentrated sulphuric acid (0·6 g.) and water (4·4 c.c.), and the cool solution diazotised by addition of sodium nitrite (0·18 g.) in water (0·9 c.c.). A cold mixture of water (1·2 c.c.) and concentrated sulphuric acid (1·2 g.) was added, and a brisk stream of sulphur dioxide passed in at 0° until a faint cloudiness began to appear. Copper powder (2 g.) was then gradually added during 40 minutes with stirring, and the mixture kept at room temperature for 2·5 hours and extracted with ether. The ethereal solution was washed with water, extracted with sodium carbonate solution, the carbonate extracts acidified (hydrochloric acid), and the sulphinic acid isolated by extraction with ether as a faintly yellow oil (0·35 g.); this was neutralised with dilute potassium hydroxide solution, the solution filtered, hydrogen peroxide (5 c.c., 100-vol.) added, and the whole evaporated to dryness on the water-bath. The residue was treated with acetone, giving the potassium salt of the sulphonic acid (I, R = Me) (0·3 g.) as a white solid. The p-*chlorobenzyl-ψ-thiouronium* derivative crystallised in colourless plates, m. p. 160—163° (Found : C, 49·7; H, 5·5. $C_{11}H_{15}O_5S,C_8H_9N_2ClS$ requires C, 49·4; H, 5·5%).

Methylation of Dihydroeugenol-5-sulphonic Acid.—Potassium dihydroeugenol-5-sulphonate (0·5 g.) was dissolved in water (5 c.c.), potassium hydroxide (0·5 g.) in water (2 c.c.) added, followed by methyl sulphate (0·5 g.), and the mixture was refluxed for 8 hours. Further additions of potassium hydroxide and methyl sulphate were made until methylation was complete (*ca.* 24 hours). The product was neutralised (hydrochloric acid) and evaporated to dryness. The residue was fractionally crystallised from water to remove potassium sulphate and gave potassium methyldihydroeugenol-5-sulphonate (0·1 g.). The *p*-chlorobenzyl-*ψ*-thiouronium derivative formed colourless plates, m. p. 160—163°, identical with the compound above.

O-*Methyldihydroeugenol-6-sulphonic Acid* (II, R = Me).—The 6-sulphinic acid, prepared from 6-amino-*O*-methyldihydroeugenol (0·5 g.) as in the case of the 5-acid (except that hydrochloric acid was used instead of sulphuric), was dissolved in baryta solution and neutralised (sulphuric acid), the solution filtered, hydrogen peroxide (4 c.c.) added, and the solution evaporated to dryness; treatment of the residue with acetone afforded the barium methyldihydro-salt of the acid (II, R = Me) (0·2 g.). The *p*-chlorobenzyl-*ψ*-thiouronium derivative formed white needles, m. p. 158° (after sintering at 145—147°) (Found : C, 49·8; H, 5·4%) (cf. above).

Methylation of Dihydroeugenol-6-sulphonic Acid (II, R = H).—The potassium salt (0·1 g.) was dissolved in water (1 c.c.), potassium hydroxide (40 mg.) and methyl sulphate (50 mg.) added, and the mixture refluxed for 2·5 hours. The product was neutralised (hydrochloric acid) and concentrated, the potassium salt of (II, R = Me) separating; it recrystallised from water in colourless needles (50 mg.). The benzyl- and the *p*-chlorobenzyl-*ψ*-thiouronium derivative formed colourless needles, m. p. 185° and 156° (sinters 146°), respectively, identical with the corresponding derivatives prepared above.

Sulphonation of O-*Methyleugenol.*—*O*-Methyleugenol (6 c.c.) was dropped into well-stirred concentrated sulphuric acid (15 c.c.) at 0—5° during one hour. The deep red syrup was stirred for 5 hours at room temperature and poured on ice. The mass was washed with water and sodium bicarbonate solution, the insoluble material dissolved in benzene, washed with water, dried (sodium sulphate), and the benzene removed. The residue solidified on treatment with ether to give a brown

solid (0·4 g.), which crystallised from methanol (charcoal) to give the *sultone* (IV, R = Me) of 4 : 5-dimethoxy-2-(β-hydroxy-*n*-propyl)benzenesulphonic acid in colourless prisms, m. p. 141—143° (Found : C, 51·7; H, 5·4. $C_{11}H_{14}O_5S$ requires C, 51·1; H, 5·5%).

Sulphonation of O-*Acetyleugenol*.—*O*-Acetyleugenol (7·4 g.) was added to stirred concentrated sulphuric acid (18 c.c.) at 5—10° during 30 minutes. After being stirred at 5—10° for 4 hours, the deep red product was poured on ice, and the mass washed with water and bicarbonate solution, and dried on a porous tile. The brown solid was powdered and extracted with boiling benzene. The extracts deposited a crystalline solid which recrystallised from methanol (charcoal) to give the *sultone* (IV, R = H) (" eugenol sultone ") as large colourless plates which fell to a powder after drying at 100° (0·4 g.), m. p. 166—168° [Found : C, 49·4; H, 4·8; S, 13·2; *M* (Rast), 228. $C_{10}H_{12}O_5S$ requires C, 49·1; H, 4·9; S, 13·1%; *M*, 244]. It was soluble in dilute sodium hydroxide solution. The *acetyl* derivative crystallised from benzene–light petroleum (b. p. 100—120°) in small white needles or colourless prisms, m. p. 167—169° depressed to 130—140° by the unacetylated compound (Found : C, 50·4; H, 5·0. $C_{12}H_{14}O_6S$ requires C, 50·3; H, 4·9%).

Methylation of the Sultone (IV).—The sultone (0·1 g.) was dissolved in acetone (2 c.c.), anhydrous potassium carbonate (0·11 g.) added, and the mixture refluxed with methyl sulphate (0·1 g.) for 4 hours. The acetone was removed, and the residue diluted with water; an oil separated which solidified to a white solid (0·1 g., m. p. 140—142°). This recrystallised from methanol in large colourless plates, m. p. 141—142°, identical with the sultone (IV, R = Me) above.

Action of 80% *Sulphuric Acid on* O-*Methyleugenol*.—Methyleugenol (4 c.c.) was dropped into a well-stirred mixture of water (5 c.c.) and concentrated sulphuric acid (8·7 c.c.) at 5° during two hours. Stirring was continued for a further 4 hours, ice-water was added, and the product heated to 90° for one hour. The mixture was cooled, extracted with ether, the extracts washed (sodium bicarbonate) and dried, the ether removed, and the residue distilled; it gave a colourless oil (1·85 g.), b. p. 138—140°/2 mm., which solidified on treatment with light petroleum. It crystallised from ether–light petroleum (b. p. 40—60°) to give β-3 : 4-*dimethoxyphenylisopropyl alcohol* in white leaflets (1·5 g.), m. p. 43—45° (Found : C, 67·1; H, 8·3. $C_{11}H_{16}O_3$ requires C, 67·4; H, 8·2%), which dissolved in concentrated sulphuric acid giving a deep red solution.

" *Methyleugenol Sultone* " (IV, R = Me).—β-3 : 4-Dimethoxyphenyl*iso*propyl bromide (0·5 g.) was slowly mixed with concentrated sulphuric acid (0·5 g.) at 0°. After 16 hours at room temperature, ice-water was added, unsulphonated material removed by extraction with ether, and the clear aqueous solution of the bromo-2-sulphonic acid (VIII, R = Me) so obtained was refluxed for 5 minutes. An oil separated which solidified on cooling (0·42 g.) and crystallised from methanol in colourless plates, m. p. 141—142°, identical with the sultone described above.

" *Eugenol Sultone* " (IV, R = H).—" β-Bromodihydroeugenol " (2 g.) in pyridine with acetic anhydride and acetyl chloride formed the *O*-acetyl compound as a colourless oil (1·7 g.), b. p. 142—146°/2 mm. This (0·5 g.) was mixed with concentrated sulphuric acid (0·5 g.) at 0° and the product worked up after 16 hours as in the previous sulphonation to give a clear aqueous solution of the sulphonic acid (VIII, R = H). When this was boiled for 2 minutes an oil separated which solidified on cooling (0·25 g.) and crystallised from methanol in colourless plates which fell to a powder after drying at 100°, m. p. 166—167°, identical with " eugenol sultone " described above.

One of us (J. H. T.) thanks the Colonial Products Research Council for a maintenance grant.

KING'S COLLEGE, NEWCASTLE-UPON-TYNE,
UNIVERSITY OF DURHAM.

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33. *The Replacement of the Diazonium by the Nitro-group. Part II. Extension of the Method to Nitronaphthylamines, Benzidine, and 3 : 3′-Dichlorobenzidine.*

By HERBERT H. HODGSON and EDWARD R. WARD.

Variations of procedure in Hodgson and Marsden's method (Part I, *J.*, 1944, 22) are described for working *in situ* and for avoidance of diazo-oxide formation as with, *e.g.*, 2-nitro-1-naphthylamine. The preparations of 4 : 4′-dinitrodiphenyl and 3 : 3′-*dichloro*-4 : 4′-*dinitrodiphenyl* are given.

THE general procedure of Part I has been improved. Where it is convenient to retain the cobaltinitrite *in situ* before decomposition, the diazotisation is carried out in sulphuric acid, and in many cases by Hodgson and Walker's method (*J.*, 1933, 1620), since if chlorides are present the Sandmeyer reaction might partly occur and the final product be contaminated with a difficultly removable chloro-compound. Where the diazotised amine forms a diazo-oxide in weak acid or neutral medium, the acid solution of the diazonium salt is diluted and added rapidly to an excess of aqueous sodium cobaltinitrite at 0°, which first neutralises the acid and then forms the required complex. If formation of some diazo-oxide is unavoidable, it is readily removed from the complex by digestion with ether. Hot decompositions of the complexes occur in *ca.* 10—15 minutes at 60°, but the product is sometimes impure, and when it is of low m. p. (< 120°) there is considerable tar formation, *e.g.*, in the preparation of β-nitronaphthalene,

The cobaltinitrite procedure has afforded a small yield (5%) of 1 : 2-dinitronaphthalene from 2-nitro-1-naphthylamine. Benzidine and 3 : 3′-dichlorobenzidine afforded 4 : 4′-dinitrodiphenyl and 3 : 3′-*dichloro*-4 : 4′-*dinitrodiphenyl*, respectively, in yields of *ca.* 40% and 65%. Tetrazotised *m*- and *p*-phenylenediamines did not behave normally towards sodium cobaltinitrite.

Experimental.

General Procedure.—The amine (0·05 g.-mol.), finely powdered if solid, is dissolved in a hot mixture of hydrochloric acid (20 c.c., *d*, 1·18) and water (30 c.c.), the solution chilled rapidly to obtain a finely divided precipitate of hydrochloride or free base, and the mixture cooled to below 0°; a solution of sodium nitrite (4 g.) in water (20 c.c.) is then added rapidly with vigorous stirring (total volume 100 c.c.). The filtered solution is next stirred into a mixture of chalk, ice, and a little ether (to abate frothing), and filtered at the pump into a mixture of sodium cobaltinitrite (8 g.) and water (40 c.c.) contained in the filter-flask which is gently shaken during the filtration. The formation of the precipitate of aryldiazonium cobaltinitrite is complete in about 10—15 minutes; it is then filtered off, washed with water, pressed on the filter, and washed with ether to remove any diazo-oxide from the precipitate. When freshly formed, the aromatic diazonium cobaltinitrites are bright yellow, generally insoluble in water and in ether; they are obtained in good yield (generally nearly quantitative), but vary in stability even in successive preparations, for they always darken, sometimes rapidly, in the air, and cannot be stored for long, even in the dark. They are decomposed forthwith by either a hot or a cold procedure.

Decomposition.—(*a*) The moist complex is made into a slurry with water (30 c.c.) which is gradually but vigorously stirred into a mixture of sodium nitrite (15 g.), crystallised copper sulphate (15 g.), cuprous oxide (6 g.), and water (60 c.c.) at 60—70°; decomposition is complete in about 15 minutes, and the solid is removed, washed successively with water, dilute cold sodium carbonate, and water, dried, and then either extracted with a suitable solvent or steam-distilled. The products removed by solvents are usually coloured owing to the presence of traces of azo-compounds, but they can usually be purified by dissolution in sulphuric–glacial acetic acid containing a trace of nitric acid, and reprecipitation by pouring on ice and recrystallisation.

(*b*) The complex is stirred in the cold for 24 hours, and the solid extracted by a suitable solvent or steam-distilled. The amount of tarry matter formed is less than in method (*a*), so the cold procedure appears to be preferable with complexes which yield nitro-compounds melting below 120°. Filtration after diazotisation and before neutralisation, helps filtration after neutralisation and also helps to remove substances which appear to catalyse the decomposition of the complex; the latter should be removed from the solution in which it is formed as rapidly as possible since decomposition is facilitated in this medium.

Examples of some monoamines.

Amine diazotised.	Product.	Yield, %, calc. on amine. Method (*a*).	Method (*b*).
2-Naphthylamine	2-Nitronaphthalene	45	—
4-Bromo-1-naphthylamine	4-Bromo-1-nitronaphthalene	—	10
2 : 4-Dibromo-1-naphthylamine	2 : 4-Dibromo-1-nitronaphthalene	—	2
2-Nitro-1-naphthylamine	1 : 2-Dinitronaphthalene	5	5
1-Nitro-2-naphthylamine	1 : 2-Dinitronaphthalene *	Traces	Traces
4-Nitro-1-naphthylamine	1 : 4-Dinitronaphthalene	15	30
5-Nitro-1-naphthylamine	1 : 5-Dinitronaphthalene	30	—
5-Nitro-2-naphthylamine	1 : 6-Dinitronaphthalene	—	40
6-Nitro-2-naphthylamine	2 : 6-Dinitronaphthalene	40	50
8-Nitro-2-naphthylamine	1 : 7-Dinitronaphthalene	45	40

* Cf. Veselý and Dvorák (*Bull. Soc. chim.*, 1923, **33**, 319), who failed to obtain this compound.

2-Nitro-1- and 1-nitro-2-naphthylamine were diazotised by Hodgson and Walker's method (*loc. cit.*) and the diluted, filtered solution treated with a large excess of sodium cobaltinitrite.

2 : 4-*Dibromo*-1-*nitronaphthalene* crystallised from methyl or aqueous methyl alcohol in sandy microparallelepipeds, m. p. 102° (Found: N, 4·4. $C_{10}H_5O_2NBr_2$ requires N, 4·2%), which were slightly volatile in steam, and dissolved in boiling aqueous alkali to give a yellow solution.

Examples of Some Diamines.—Benzidine. The dihydrochloride (7 g.) was stirred into a solution of hydrochloric acid (8 c.c., *d*, 1·18) and water (40 c.c.) and tetrazotised by addition of sodium nitrite (5 g.) in a little water below 8°; the mixture was neutralised with calcium carbonate as before, filtered, and the filtrate poured on sodium cobaltinitrite (8 g.) dissolved in iced water; the yield of the brilliant yellow complex was 11·5 g., *i.e.*, almost quantitative. The decomposition product obtained as above from the complex (5 g.) was washed repeatedly with water and cold sodium carbonate solution, and then boiled with 15% aqueous hydrochloric acid to remove copper salts, after which it was crystallised from boiling glacial acetic acid; yield of 4 : 4′-dinitrodiphenyl, *ca.* 20% (method *a*) and *ca.* 40% (method *b*); m. p. 233—235° (Willstätter and Kalb, *Ber.*, 1906, **39**, 3478, give m. p. 234—235°). The cobaltinitrite complex remained unaffected after two weeks' exposure to the air in daylight.

3 : 3′-*Dichlorobenzidine.* This compound (5 g.) was dissolved in a mixture of hydrochloric acid (10 c.c., *d* 1·18) and water (30 c.c.), the solution chilled rapidly, and treated below 5° with sodium nitrite (4 g.) in a little water; after neutralisation as before, the filtered solution of the tetrazo-compound was stirred with sodium cobaltinitrite (7 g.) in iced water. The yellow-orange complex (9·7 g.) was formed gradually (15 minutes) and, when removed, darkened only slightly on the surface when kept in air for 3 days. The complex (5 g.) was stirred into a cold solution of crystallised copper sulphate (8 g.) and sodium nitrite (5 g.) containing red cuprous oxide (2 g.) in suspension, decomposition being very vigorous

during the first 5 minutes with considerable frothing; the mixture was subsequently stirred for 24 hours. The 3 : 3′-*dichloro*-4 : 4′-*dinitrodiphenyl* formed (2·1 g.) was isolated as above; it crystallised three times from boiling glacial acetic acid as cream micro-needles, m. p. 226—230° (Found: N, 7·1. $C_{12}H_6O_4N_2Cl_2$ requires N, 6·9%).

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TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, June 6th*, 1946.]

NOTES.

1 : 2 : 3 : 4-*Tetrahydro*isoquinaldinic *Acid*. By W. SOLOMON.

iso*Quinaldinic Acid*.—1-Cyano-2-benzoyl-1 : 2-dihydro*iso*quinoline, obtained from *iso*quinoline, benzoyl chloride, and aqueous potassium cyanide (Reissert, *Ber.*, 1905, **38**, 3427), is best hydrolysed to *iso*quinaldinic acid by boiling with 10 vols. of 65% sulphuric acid for 2 hours (cf. Padbury and Lindwall, *J. Amer. Chem. Soc.*, 1945, **67**, 1269). The crude yield in the form of copper salt is 83%. The free acid is best crystallised from 7—8 parts of hot water. The yield of the acid so purified, calculated on the original cyano-compound, is 58%; m. p. 168—171° (froths).

1 : 2 : 3 : 4-*Tetrahydro*isoquinaldinic *Acid*.—*iso*Quinaldinic acid (24 g.) in glacial acetic acid (288 c.c.) at atmospheric pressure and *ca.* 50°, absorbed, in the presence of Adams's platinum oxide catalyst (1·6 g.), the calculated volume of hydrogen (6·5 l. at N.T.P.) in 13 days' intermittent shaking. The catalyst had to be highly active to effect even this rate of absorption. After filtration and removal of solvent under reduced pressure, the residue was triturated with alcohol and the resulting solid collected and washed with alcohol. Only 15·9 g. were obtained, the filtrate containing a further 10·5 g. of uncrystallisable material whose nature at present remains unknown. The solid, on crystallisation from a boiling mixture of alcohol (10 vols.) and water (20 vols.), furnished the *tetrahydro-acid* in colourless plates, m. p. 299° (decomp.) after softening (Found: C, 67·7; H, 6·3; N, 7·55. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3; N, 7·9%). The N-*benzoyl* derivative, obtained by the method of Steiger (*J. Org. Chem.*, 1944, **9**, 396), separated from alcohol in hard, dazzlingly white incrustations of colourless plates, m. p. 120° (decomp.) after sintering at 110° (Found: C, 72·4; H, 5·6; N, 4·9. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·4; N, 5·0%). This derivative, on esterification with methanol and sulphuric acid, furnished *methyl* N-*benzoyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinaldinate, large transparent prisms, m. p. 105—108°, from methanol, sparingly soluble in ether, but readily in other solvents (Found: C, 73·4; H, 5·8; N, 4·8. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8; N, 4·7%).

The author's thanks are due to Messrs. A. W. Stokes and H. Waddington for experimental assistance and to Mr. A. Bennett for the micro-analyses.—WELLCOME LABORATORIES OF TROPICAL MEDICINE, LONDON, N.W.1. [*Received, April 18th*, 1946.]

Diglycylethylenediamine. By T. L. COTTRELL and J. E. GILL.

PFEIFFER and SAURE (*J. pr. Chem.*, 1941, **157**, 116) obtained, by ammonolysis of bischloroacetylethylenediamine under fairly drastic conditions, a compound which they considered to be diglycylethylenediamine. They reported a viscous oil, which on long standing gave hygroscopic crystals. No m. p. or analytical figures were given, and it was characterised as the picrate, m. p. 238—241°.

We have obtained diglycylethylenediamine as a crystalline, non-hygroscopic material in good yield. The difference between our method of preparation and that of Pfeiffer and Saure was in the use of milder conditions of ammonolysis (cf. Cheronis and Spitzmueller, *J. Org. Chem.*, 1941, **6**, 349), and in the method of isolation of the base from the hydrochloride. For this they used silver oxide, but we noted that the base tended to form a soluble silver complex.

The compound was strongly basic; its behaviour with copper hydroxide was similar to that of the compound described by Pfeiffer and Saure.

Experimental.—Bischloroacetylethylenediamine. Bergell's method (*Z. physiol. Chem.*, 1922, **123**, 280) for the preparation of this compound gave only a 14% yield, so the following method was adopted. 22·7 G. of chloroacetyl chloride, dissolved in 60 ml. of dry chloroform, were added slowly with cooling and stirring to 14·7 g. of ethylenediamine in 100 ml. of dry chloroform. The solid was filtered off and extracted with hot absolute alcohol to give 15·2 g. of crude bischloroacetylethylenediamine. This was recrystallised from absolute alcohol, giving 12·5 g. (59%) of pure compound, m. p. 175° (Bergell gives m. p. 171—172°). The compound could also be prepared from chloroacetic ester and ethylenediamine.

Diglycylethylenediamine. A mixture of 14·1 g. of the foregoing compound, 105 g. of ammonium carbonate in 90 ml. of water, and 120 ml. of ammonia (*d* 0·88) was kept at room temperature for 18 hours, heated to 55° for 4 hours, and then filtered. The clear filtrate was evaporated to dryness under reduced pressure and extracted with 300 ml. of absolute alcohol under reflux. The residue was dissolved in the minimum quantity of water, and poured into 200 ml. of absolute alcohol. The precipitate, which consisted of the crude hydrochloride, was filtered off (11·7 g., 70%). Recrystallised from aqueous alcohol, it had m. p. 246° (decomp.).

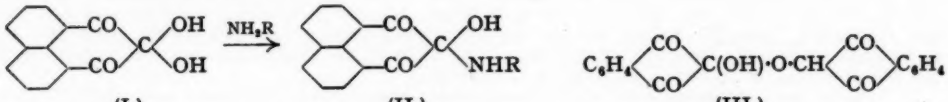
7 G. of the hydrochloride were converted into the base by adding 57 ml. of N-sodium hydroxide solution, evaporating to dryness, and extracting the residue with butanol. The base, crystallised from butanol, had m. p. 157—158° (yield theoretical) (Found: C, 41·3; H, 8·03; N, 31·4. Calc. for

$C_6H_{14}O_2N_4$: C, 41·3; H, 8·05; N, 32·2%) and formed non-hygroscopic needles. The picrate had m. p. 240° (decomp.). The acetyl derivative, recrystallised from aqueous alcohol or water, had m. p. 278—279° (Found: Ac, 32·6. Calc. for $C_{10}H_{18}O_4N_2$: Ac, 33·3%).

Attempts to prepare diglycylethylenediamine by condensation of ethylenediamine with glycyl chloride or glycine were unsuccessful. From glycine ester a very small yield of the substance was obtained.—IMPERIAL CHEMICAL INDUSTRIES LIMITED, EXPLOSIVES DIVISION, RESEARCH DEPARTMENT, STEVENSTON, AYRSHIRE. [*Received, April 25th*, 1946.]

Derivatives of peri*Naphthindanetrione.* By RADWAN MOUBASHER and (MRS.) AKILA MOSTAFA.

ERRERA and SORGES (*Gazzetta*, 1913, **43**, ii, 625) stated that aniline reacts with *peri*naphthindane-1 : 2 : 3-trione hydrate to form a substance believed to be (II, R = Ph), but they did not describe the substance apart from stating that it decomposes on heating. We obtained this compound in intense yellow crystals and also the p-*chloroaniline* analogue. With benzidine a *substance* was obtained formed by condensation of equimolecular amounts. Alkaline hydrolysis in the presence of air produced naphthalic acid and aniline, *p*-chloroaniline, or benzidine, respectively. Acid hydrolysis afforded the bases together with the trione hydrate.



(I.) (II.) (III.)

Schönberg and Moubasher (*J.*, 1944, 366) showed that triketohydrindene is photochemically reduced in sunlight by *iso*propyl alcohol to the colourless product (III; see Ruhemann, *J.*, 1911, **99**, 797), and we find that *peri*naphthindanetrione behaves similarly, giving a colourless product (isolated as a *dihydrate*) believed to be of analogous structure, although a symmetrical constitution, >C(OH)·C(OH)<, is not excluded.

Action of peri*Naphthindane*-1 : 2 : 3-*trione Hydrate on Bases.*—(*a*) *Aniline.* The hydrate (1 g.), dissolved in water at room temperature, was treated dropwise with aniline (6 g.). Yellow needles were formed almost at once, and after standing for a short time the 2-anilino-2-hydroxy*peri*naphthindane-1 : 3-dione (II, R = Ph) was filtered off and crystallised from 50% alcohol; m. p. about 230° (decomp.), depending on the rate of heating; yield, 1·3 g. (Found: C, 75·6; H, 4·4; N, 4·7. Calc. for $C_{19}H_{13}O_3N$: C, 75·2; H, 4·3; N, 4·6%).

(*b*) p-*Chloroaniline.* The 2-p-*chloroanilino*-analogue, similarly prepared, formed yellow crystals, m. p. 220°; yield, 1·5 g. (Found: C, 66·9; H, 3·5; N, 3·9; Cl, 10·5. $C_{19}H_{12}O_3NCl$ requires C, 67·5; H, 3·6; N, 4·1; Cl, 10·5%).

(*c*) *Benzidine.* The reaction was carried out in a mixture of equal volumes of water and alcohol, containing *peri*naphthindane-1 : 2 : 3-trione (1 g.) and benzidine (0·82 g.). 2-*Benzidino*-2-*hydroxy*peri*naphthindane*-1 : 3-*dione* (II, R = $C_6H_4{\cdot}C_6H_4{\cdot}NH_2$) was crystallised from ethyl alcohol; m. p. 270° (decomp.); yield, 1·4 g. (Found: C, 75·6; H, 4·6; N, 7·0. $C_{25}H_{18}O_3N_2$ requires C, 76·1; H, 4·6; N, 7·1%).

The first two compounds were soluble in benzene and alcohol, and the last in the hot solvents. The colours given in concentrated sulphuric acid were, respectively, an intense violet, green, and red.

Hydrolysis of Condensation Products.—(*a*) *In acid solution.* 1 G. of the substance was refluxed with a mixture of 25 c.c. of hydrochloric acid (*d* 1·1) and 25 c.c. of water for 15 minutes. On cooling, colourless crystals of the trione hydrate were obtained, which after crystallisation had m. p. and mixed m. p. 273°. The solution contained aniline, *p*-chloroaniline, or benzidine.

(*b*) *In alkaline solution.* 1 G. of the substance was refluxed for 15 minutes with aqueous sodium hydroxide solution (10%; 50 c.c.), and the blue solution was cooled and decolorised by shaking with air. The mixture was extracted with ether, and the extract, on evaporation, yielded aniline, *p*-chloroaniline, or benzidine. The aqueous solution in each case on acidification yielded naphthalic acid (m. p. and mixed m. p. 274° after crystallisation from benzene).

Photo-reduction of peri*Naphthindane*-1 : 2 : 3-*trione with* iso*Propyl Alcohol.*—The trione (2 g.) was suspended in freshly distilled *iso*propyl alcohol (10 c.c.) in a sealed "Pyrex" tube, in an atmosphere of carbon dioxide. The tube was exposed to sunlight for a week (in April). The resulting yellow solid was filtered off, and the excess of alcohol evaporated in a vacuum. The solid mass recrystallised from benzene to form pale yellow needles of a *dihydrate* (1·1 g.), m. p. 220° (decomp.), soluble in alcohol and acetic acid (Found: C, 67·6; H, 3·9. $C_{16}H_{14}O_6.2H_2O$ requires C, 68·1; H, 3·9%).

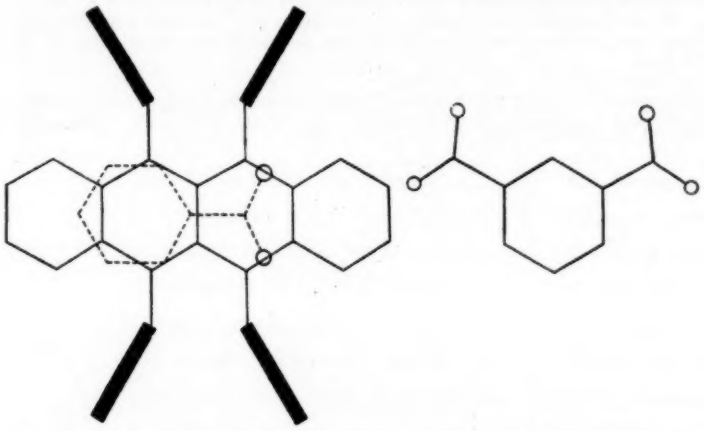
The photo-product (0·5 g.) was refluxed with 25 c.c. of sodium hydroxide solution (20%) for 15 minutes. The blue solution was cooled, and shaken with air until decolorised; from this solution naphthalic acid (identified as above) was obtained. The same acid (m. p. and mixed m. p. 274°) was isolated as a colourless sublimate when the photo-product was heated with selenium in a stream of oxygen at 220° (bath temp.).—FOUAD I UNIVERSITY, CAIRO, EGYPT. [*Received, April 26th*, 1946.]

Stereo-effects and van der Waals Complexes. By E. J. BOWEN and E. COATES.

The quenching of the fluorescence of aromatic hydrocarbons in solution by other aromatic molecules is often due to the formation of comparatively stable van der Waals complexes (Bowen, Barnes, and Holliday, *Trans. Faraday Soc.*, 1946, to appear), and in other cases, where the life of the complex is very short, to collisions governed by diffusion. We find that the quenching of the fluorescence of rubrene

in hexane solution by nitrobenzene arises from complex formation with a heat of formation of 2·5 k.-cals./mole, and *m*-dinitro- and *s*-trinitro-benzene behave as collisional quenchers. The reason for this difference in behaviour, which is the opposite of that which would be expected at first sight from the work of Briegleb (*Z. physikal. Chem.*, 1932, *B*, **19**, 255; 1934, *B*, **26**, 63; 1935, *B*, **27**, 474; 1935, *B*, **31**, 58; 1936, *B*, **32**, 305) on the stability of hydrocarbon–nitro-compound complexes, is apparent from the figure. The nitrobenzene molecule can accommodate itself parallel to the naphthacene centre of

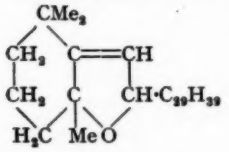
Rubrene and Nitrobenzene. m-*Dinitrobenzene.*



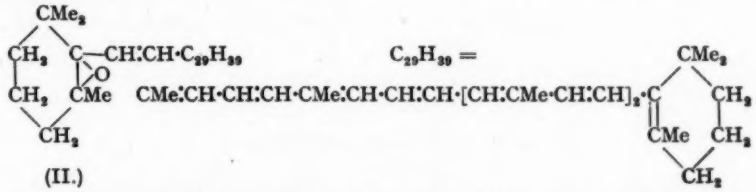
the rubrene molecule, but the polynitro-compounds cannot because of interference from the four phenyl groups which are not coplanar with the centre. This affords further evidence of the structure of hydrocarbon–nitro-compound complexes as parallel molecular orientations.—PHYSICAL CHEMISTRY LABORATORY, SOUTH PARKS ROAD, OXFORD. [*Received, May 22nd*, 1946.]

The Pro-vitamin-A Activity of Mutatochrome. By N. T. GRIDGEMAN, R. F. HUNTER, and N. E. WILLIAMS.

MUTATOCHROME (I) (Karrer and Jucker, *Helv. Chim. Acta*, 1945, **28**, 27), which Euler, Karrer, and Walker (*ibid.*, 1932, **15**, 1507) originally supposed to be β-carotene epoxide (" β-carotene oxide ") (II), shows growth-promoting activity in rats not closely similar to that of β-carotene as stated by the original authors but appreciably less than that of α-carotene.



(I.)



(II.)

This result and the 1 : 2 ratio for biological activity of α- to β-carotene (Kuhn and Brockmann, *Klin. Wochenschr.*, 1933, **12**, 972; Kuhn, Brockmann, Scheunert, and Schieblich, *Z. physiol. Chem.*, 1933, **221**, 129; Wilkinson, *Biochem. J.*, 1941, **35**, 824) are consistent with the view that the conversion of β-carotene into vitamin-A which occurs *in vivo* involves the fission of the central double bond in the former (cf. Hunter, *Chem. and Ind.*, 1942, **61**, 89). Similar but less precise evidence on the same point is furnished by the earlier observations of Kuhn and Brockmann (*Ber.*, 1933, **66**, 1319) and Kuhn and Grundmann (*Ber.*, 1934, **67**, 593) that semi-β-carotenone and cryptoxanthin show growth-promoting activity in daily doses of 5—10 μg. in contrast to β-carotene which is effective in doses of 2·5 μg.

Experimental.—The following experiment on the preparation of mutatochrome is typical:

A solution of β-carotene (0·55 g.) in chloroform (100 c.c.) was treated with perbenzoic acid in the same solvent (1·2 mols.; 3·2 c.c.) and kept at 0° in an atmosphere of carbon dioxide for 42 hours. The solution was washed with aqueous sodium bicarbonate (5%), dried (Na_2SO_4), and evaporated under reduced hydrogen pressure with the usual precautions (Hunter and Scott, *Biochem. J.*, 1941, **35**, 31) at a temperature below 50°. The mutatochrome, which was separated by chromatography on alumina as a typical lemon-yellow zone, was rechromatographed and crystallised from acetone, from which it separated in small yellow-brown crystals, m. p. 158°, which showed absorption maxima at 487 and 456mμ in carbon disulphide and at 464 and 437mμ in chloroform ($E^{1\%}_{1\,cm.}$ = 1910 and 2190, respectively, for latter solvent). It showed a transient band at 5950 A. in the antimony trichloride reaction.

The yield of mutatochrome varied from 5 to 12% but attempts to increase this by variation of concentration of perbenzoic acid, temperature, and time proved unsuccessful (cf. Euler, Karrer, and Walker, *loc. cit.*).

Biological assay. Mutatochrome was dissolved in refined deodorised arachis oil containing 0·01% of quinol and the pro-vitamin-A activity of the solution in Wistar rats was compared with that of the International Standard preparation (1934) of β-carotene diluted with arachis oil. A total of 87 vitamin-A deficient rats, in 27 isogenic sets (11 tetrads, 11 triads, and 5 pairs), was used in a 4-point experimental design (Gridgeman, *Biochem. J.*, 1943, **37**, 127), with daily doses of (i) 0·54 μg. mutatochrome, (ii) 0·72 μg. β-carotene, (iii) 0·9 μg. mutatochrome, and (iv) 1·2 μg. β-carotene over a 3-week period. As group (i) grew less than group (ii) and group (iii) less than group (iv), it was at once obvious that the mutatochrome was appreciably less than 75% as potent as β-carotene. The actual assay, expressed as weight for weight activity of mutatochrome in terms of β-carotene, was 39%, the ($P = 0·95$) fiducial limits of error being 29 to 47%. As the International Standard preparation of β-carotene is known to be less than 100% pure, mutatochrome has certainly less than 47%, and probably less than 39%, of the pro-vitamin-A activity of β-carotene.

We thank the Directors of Lever Brothers and Unilever Ltd. for permission to publish these results.—
RESEARCH DEPT., LEVER BROTHERS AND UNILEVER LTD., PORT SUNLIGHT. [*Received, May 1st*, 1946.]